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The American Journal of Medicine

Vol. XVI APRIL, 1954 No. 4

Editorial

Intravascular Resistance . . . . . MILTON MENDLOWITZ 465

Clinical Studies

Studies on the Mechanism of Ventricular Activity

VI. The Depolarization Complex in Pure Subendocardial Infarction; Role of the Subendocardial Region in the Normal Electrocardiogram
MYRON PRINZMETAL, CLINTON MCK. SHAW, JR., MORTON H. MAXWELL, EILEEN J. FLAMM, ALFRED GOLDMAN, NOBORU KIMURA, LOUIS RAKITA, JEAN-LOUIS BORDUAS, SOL ROTHMAN AND REXFORD KENNAMER 469

VII. The Origin of the Coronary QR Wave
CLINTON MCK. SHAW, JR., ALFRED GOLDMAN, REXFORD KENNAMER, NOBORU KIMURA, INGA LINDGREN, MORTON H. MAXWELL AND MYRON PRINZMETAL 490

In the first article Dr. Prinzmetal and his associates re-examine the controversial question of the electrocardiographic manifestations of "pure" subendocardial infarction by producing such lesions (with subsequent necropsy confirmation) in dogs and recording appropriate precordial and epicardial leads. No abnormal Q waves appeared so long as the outer ventricular layers remained intact; further investigation including oscillographic measurements of the rates of intramural depolarization at inner and outer ventricular layers, explained why abnormal Q waves are not recorded under these circumstances. The authors re-affirm the view that subendocardial damage limited to the inner ventricular myocardium ordinarily does not register in clinical electrocardiography, a serious limitation in diagnosis of myocardial infarction in man.

The second paper deals with the conditions necessary for appearance of a coronary QR wave. Coronary artery ligation experiments in dogs indicated that such abnormal waves occurred only when the superficial ventricular layers suffered damage resulting in the presence there of both live and dead muscle. On the basis of this observation the clinical significance of various types of QRS changes recorded after coronary artery occlusion in man is discussed at length.

Metabolism of the Human Heart. II. Studies on Fat, Ketone and Amino Acid Metabolism . . . . R. J. BING, A. SIEGEL, I. UNGAR AND M. GILBERT 504

Dr. Bing and his colleagues continue their ingenious experiments employing the technic of catheterization of the coronary sinus for *in vivo* study of the metabolism of the heart in man. The utilization of fatty acids, ketones and amino acids was investigated, with results indicating that all these substances can be used by the cardiac muscle as sources of energy. These conclusions appear to be well founded despite the many assumptions necessary and the large scatter observed; more-

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Hunter, C.: Canad. M. A. J. *30*:41 (Jan.) 1934.

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Best, R. R.; Hicken, N. F., and Finlayson, A. I.: Ann. Surg. *110*:67, 1939.

1946 — In chronic cholecystitis, "the bile acid of choice is dehydrocholic acid...."
Cheney, G., in Reimann, H. A.: Treatment in General Medicine, ed. 2, Philadelphia, F. A. Davis Company, 1941, vol. 1, p. 851.

1950 — "...Liberal quantities of Decholin...will be found advantageous in stimulating the flow of bile and promoting better drainage after operation."
Sanders, R. L.: Am. J. Surg. *72*:811, 1946.

1952 — "If the therapeutic aim is to flush the bile duct with a free-flowing, thin bile...dehydrocholic acid is administered...."
Cranshaw, J. F.: Am. J. Digest. Dis. *17*:387, 1950.

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Beckman, H.: Pharmacology in Clinical Practice, Philadelphia, W. B. Saunders Company, 1952, p. 361.

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O'Brien, G. F., and Schweitzer, I. L.: M. Clin. North America *37*:155 (Jan.) 1953.

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over, preferential myocardial usages could be established and semi-quantitative estimates obtained. Thus a number of points of general as well as specifically cardiac interest emerge from this provocative study.

Effect of Banthine on the Cardiac Mechanism in States Associated with Increased Vagal Tone . . . . . THOMAS HAYMOND AND SAMUEL BELLET 516

Banthine and probanthine given intravenously or orally are shown to exert beneficial atropine-like, cholinergic blocking effects in cardiovascular states characterized by increased vagal tone. Of particular interest is the abolition of hypersensitive carotid sinus syndrome by oral administration of banthine. Unpleasant side reactions appear to be fewer than with therapeutically equivalent doses of atropine.

Pulmonary Stenosis with Left to Right Intracardiac Shunts
GEORGE R. MOFFITT, JR., HARRY F. ZINSSER, JR., PETER T. KUO, JULIAN JOHNSON AND TRUMAN G. SCHNABEL, JR. 521

The authors cite six cases illustrating pulmonary stenosis with atrial or ventricular septal defects in which the predominant shunt, at least at rest, is from left to right, with absence of significant cyanosis. The question raised is whether pulmonary valvulotomy is indicated in such patients or should be restricted, for the present, to pulmonary valvular stenosis with marked elevation of the right ventricular pressure and predominant right to left intracardiac shunt.

Tuberculosis and Congenital Cyanotic Heart Disease
ROBERT D. SLOAN, C. ROLLINS HANLON AND H. WILLIAM SCOTT, JR. 528

This collaborative study deals in particular with two points: the incidence of pulmonary tuberculosis in congenital cyanotic heart disease, said to be high but found by the authors in a large series of cases not to be excessive; and the danger of lighting up obsolescent pulmonary tuberculous lesions in such cases by surgery circumventing pulmonary stenosis and thus encouraging the growth of M. tuberculosis by increased blood oxygenation. If the latter consideration does present a real hazard, there was no indication of it in the cases studied.

Bacterial Endocarditis. An Analysis of Fifty-two Cases
WALTER NEWMAN, JOSE M. TORRES AND JOHN K. GUCK 535

The introduction of antibiotic therapy has so altered the diagnostic as well as therapeutic approach to bacterial endocarditis that this analysis of current experience in fifty-two cases is particularly timely. The need for less rigid criteria for institution of therapy on the basis of presumptive, not necessarily definitive, diagnosis is stressed. The increased incidence of associated congestive heart failure is discussed, as are many other points of interest. Perhaps the most striking datum deals with the "cure" rate. Sterilization of the blood was effected in two-thirds of the cases but of the

Contents continued on page 7



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"cures" one-third eventually died of sequelae of the disease, one-third are alive but disabled and only one-third are alive and asymptomatic. This experience is probably fairly representative and indicates that often treatment is still too little and too late.

Mechanism of Formation of Left Auricular Mural Thrombi
JACQUES B. WALLACH, LESLIE LUKASH AND ALFRED A. ANGRIST 543

In view of the growing significance of auricular mural thrombi in both the medical and surgical management of rheumatic heart disease, this discussion of the factors operative in the formation of such thrombi is particularly timely. The authors consider the mechanical effects of impingement of a regurgitant jet upon the auricular wall, auricular fibrillation, alterations in clotting mechanism, auricular infarction and persistent rheumatic activity in the auricular myocardium among the factors to be taken into account.

Effects of Vigorous Physical Exercise on Cerebral Circulation and Metabolism
PERITZ SCHEINBERG, L. IONE BLACKBURN, MAURICE RICH AND MILTON SASLAW 549

Although ingenious methods of investigation have been devised, the physiologic pattern of cerebral vascular tone regulation has not been worked out fully. In the present study vigorous physical exercise was employed to produce metabolic acidosis, with consequent decrease in arterial blood CO_2 content and pH but without significant change in arterial pCO_2. No correlation could be made out between the degree of these changes and the marked alterations in cerebral circulatory and metabolic functions which occurred with exercise.

Review

Polyps of the Colon and Rectum. Their Incidence and Relationship to Carcinoma
J. ALFRED RIDER, JOSEPH B. KIRSNER, HUGO C. MOELLER AND WALTER L. PALMER 555

A common and particularly vexing problem is what to do with the patient in whom colonic polyps are discovered coincidentally in the course of x-ray or sigmoidoscopic examination. This problem, which revolves largely upon the risk of associated malignancy, is not resolved by the present study but factual data in a large series are offered. It seems clear that when local removal is possible this is indicated. Generalization in other circumstances is difficult.

Seminars on Liver Disease

Meaning of Liver Function Tests . . . . . FRANKLIN M. HANGER 565

Dr. Hanger contributes a sober analysis of the underlying significance and the limitations in usefulness of some of the measurements of liver function in general use: hyperbilirubinemia, serum proteins including those responsible for the cephalin flocculation reaction, serum alkaline phos-

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phatase, bromsulfalein, blood cholesterol, serum enzymes. The discussion takes into account some of the latest developments in this field and the thoughtful reader will find this a most rewarding essay.

Conference on Therapy

Drugs in the Diagnosis of One of the Curable Forms of Hypertension 574

Conferences on Therapy (Cornell University Medical College)—The clinical consequences of pheochromocytoma being remediable by removal of the offending tumor, the problems of diagnosis assume considerable practical importance even though this is a rare cause of hypertension. The present conference deals chiefly with the usefulness and limitations of so-called adrenergic blocking agents, particularly Regitine and benzodioxane; the applicability of recently developed tests for measurement of catecholamine excretion in the urine also is discussed.

Clinico-pathologic Conference

Fever of Unknown Origin 581

Clinico-pathologic Conference (Washington University School of Medicine)—The problem of fever of indeterminate origin is always with us, and the discussion of this case follows a standard pattern. The findings at necropsy serve as a reminder both of the frequency and elusiveness of the symptom-complex of which this case is a good example.

Research Society Abstracts

Southern Society for Clinical Research—Abstracts of Papers Presented at the Seventh Annual Meeting, New Orleans, Louisiana, January 30, 1954 590

Case Report

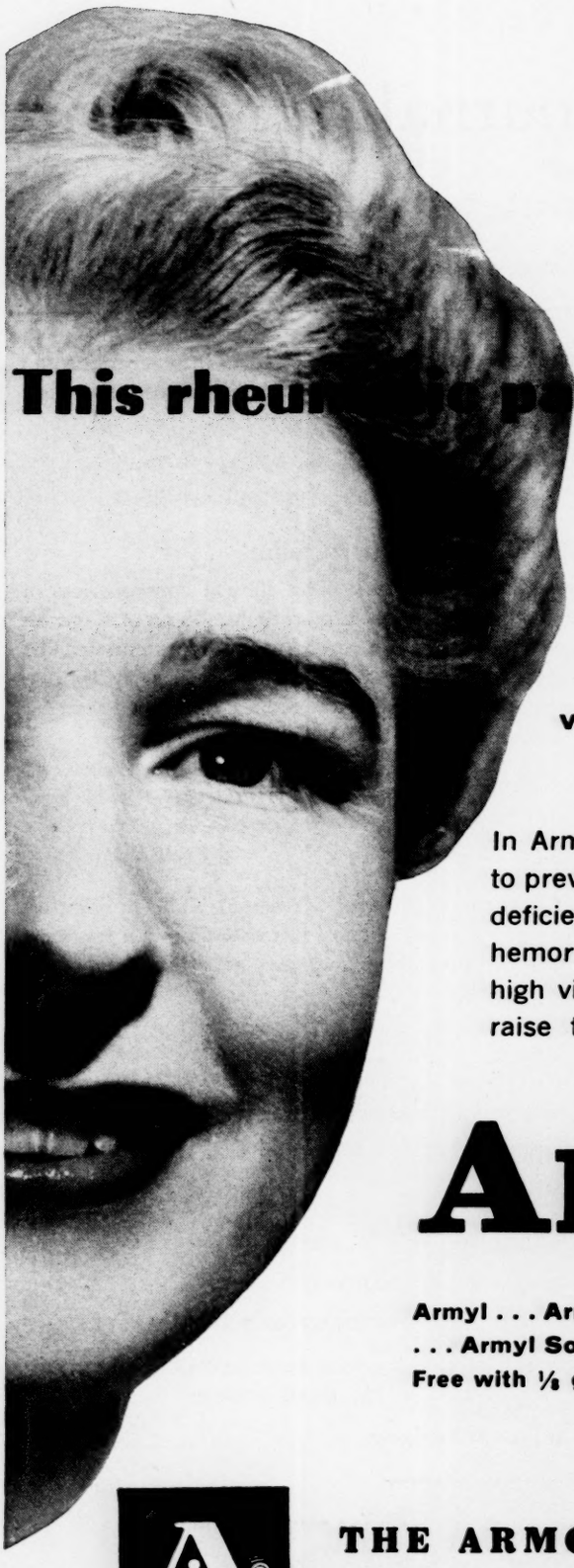
Dystrophia Myotonica with Associated Sprue-like Symptoms

K. K. KAUFMAN AND E. W. HECKERT 614

A concise description of a classic case of myotonic dystrophy, with associated sprue-like symptoms and laboratory findings attributable to involvement of the small intestine.

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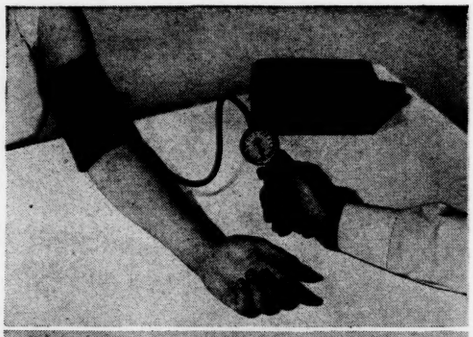
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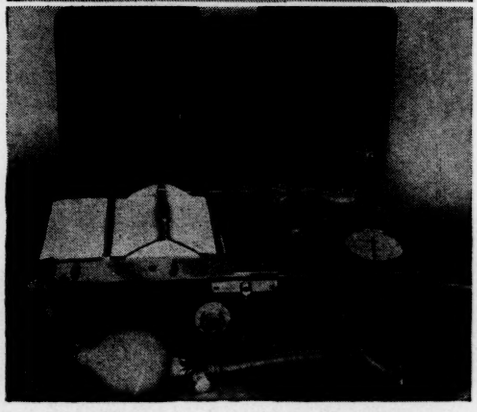
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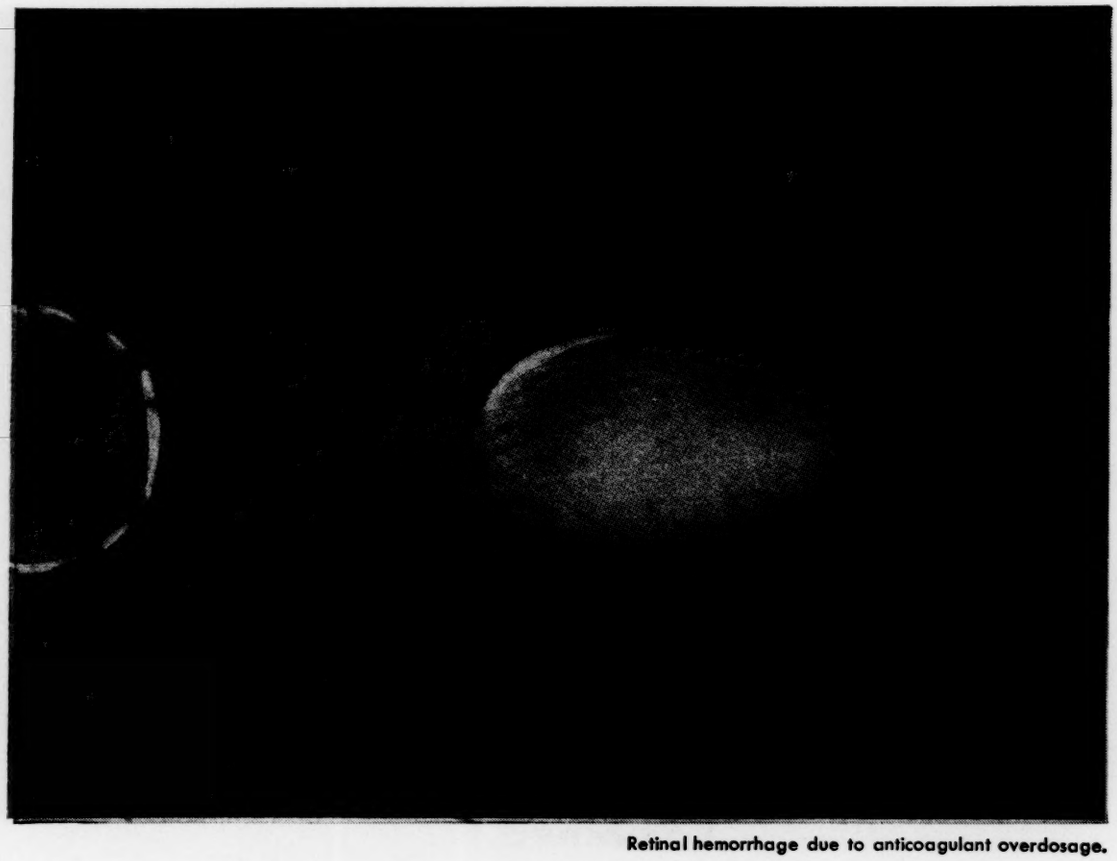
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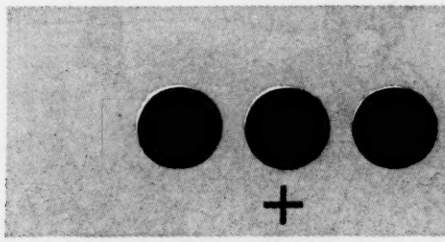

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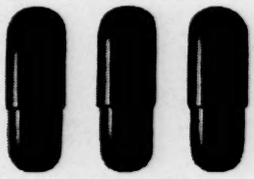
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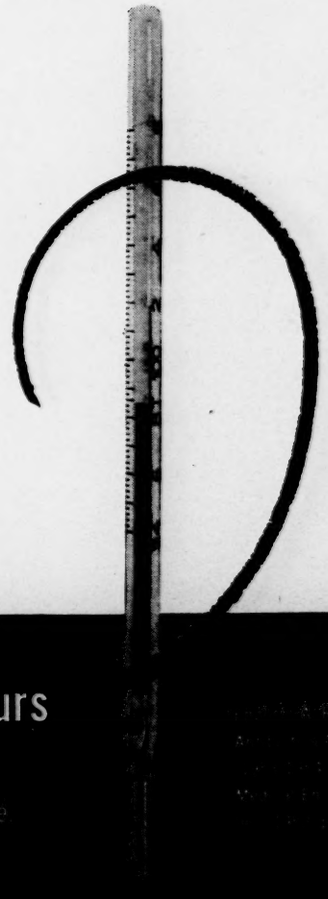
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The dietary regimen used in this study provided a protein in the ration deficient in the sulfur amino acids cited. This regimen increased serum cholesterol concentration to 300 to 800 mg. per cent and led to vascular lesions. These lesions "were in the ascending aorta but extended from the valves to the left ventricle to the proximal portions of the carotid and femoral arteries. Minimal lesions . . . [were] observed in the coronary arteries. The aortic lesions were . . . characterized by the presence of lipid-laden phagocytes and increase in collagen and elastic fibers. The lipids were in part cholesterol derivatives."

The study reports further that the hypercholesterolemia due to the dietary deficiency of sulfur amino acids "could be largely prevented by feeding 1 Gm. per day of dl-methionine or 1-cystine as supplements to the diet. After the serum concentration had become elevated, it could be restored to normal by feeding 1 Gm. of dl-methionine . . . daily."

As the authors state, it would be both naive and premature today to attribute human atherosclerosis to deficiency of an amino acid. However, even though only foreshadowing applicability in the human realm, the findings in this study reemphasize the vital role, realized and potential, which *complete* protein plays in metabolism.

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*Mann, G. V.; Andrus, S. B.; McNally, A., and Stare, F. J.: Experimental Atherosclerosis in Cebus Monkeys, J. Exper. Med. 98:195 (Sept.) 1953.

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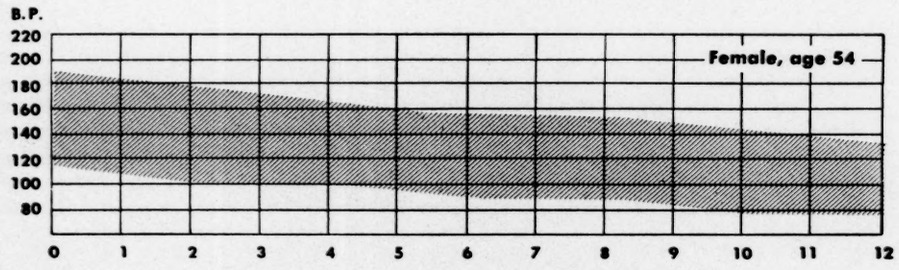
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Rauwolfia serpentina

IN COMBINATION

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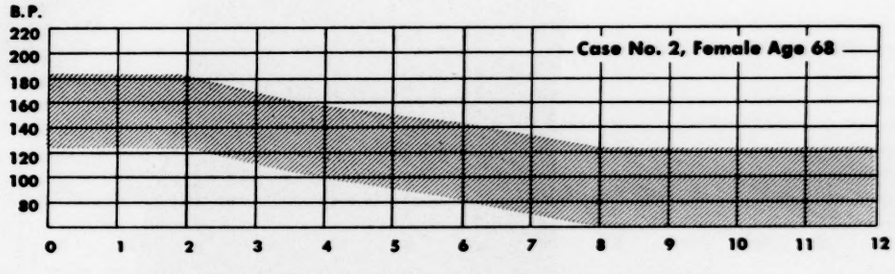
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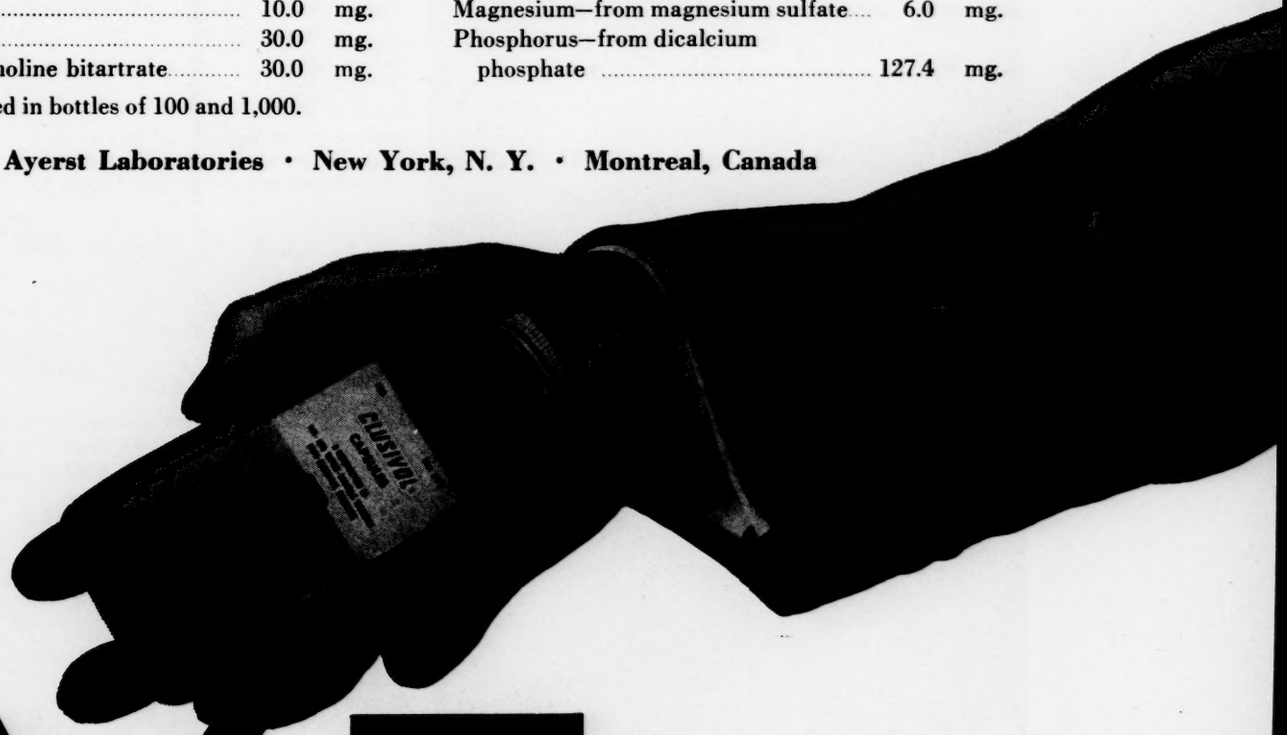
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1. Reich, C., and Mulinos, M. G., Treatment of Refractory Nutritional Anemia with Gelatine. Bull. N. Y. Med. Coll. March 1953.

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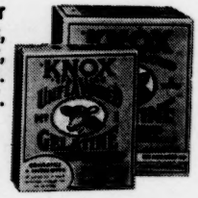
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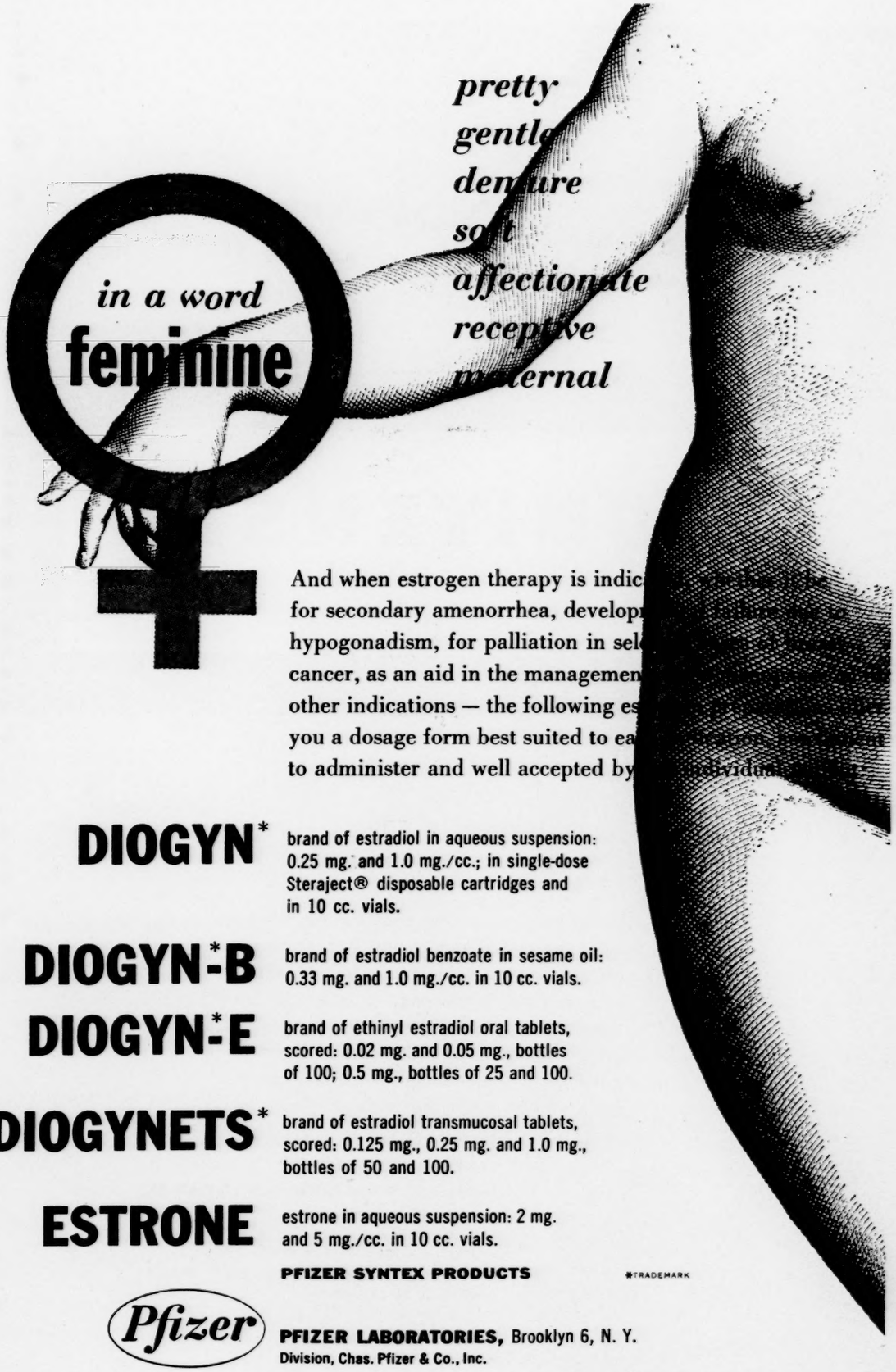
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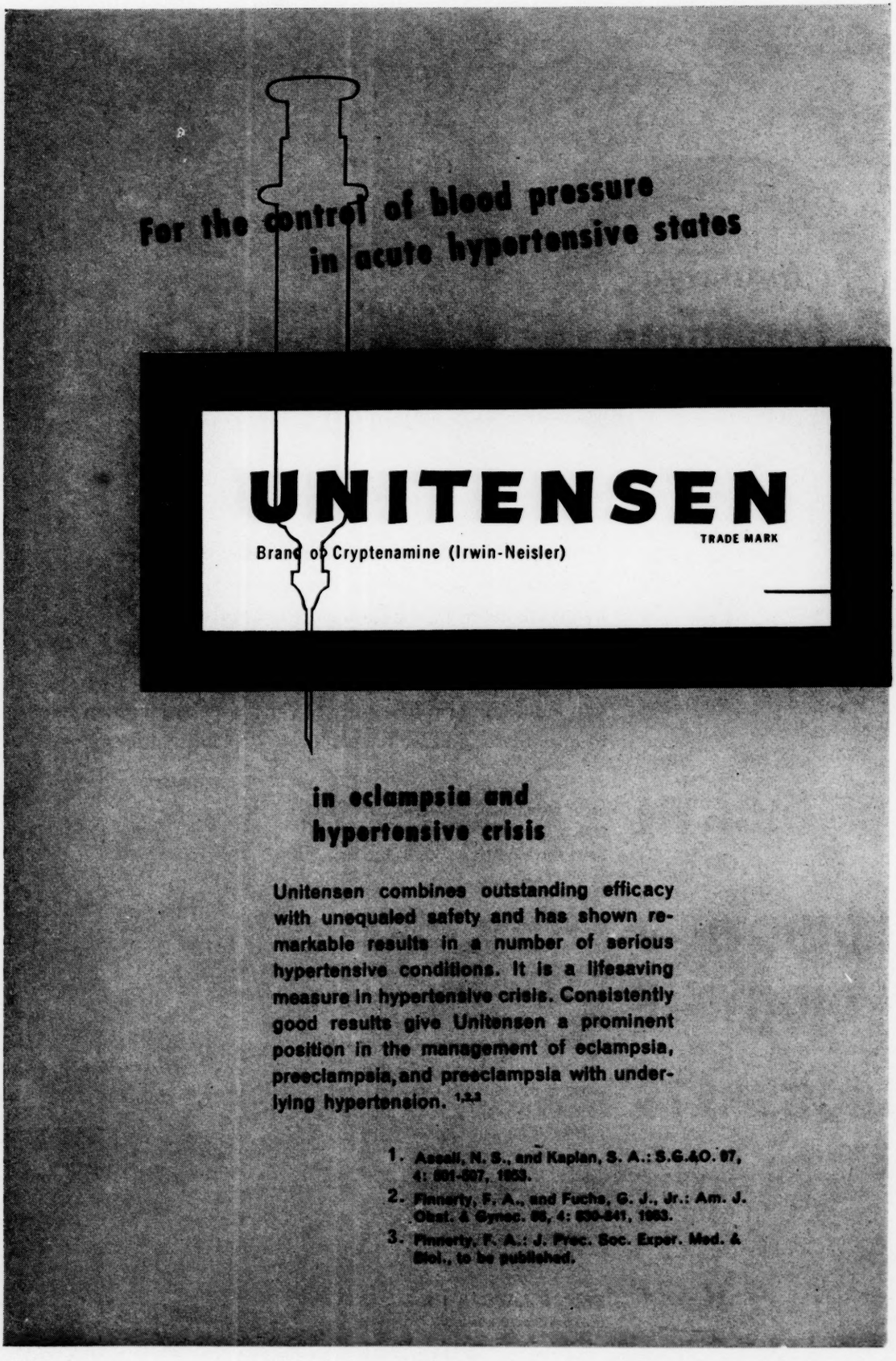
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1. Assali, N. S., and Kaplan, S. A.: S.G.&O. 97, 4: 501-507, 1953.
2. Finnerty, F. A., and Fuchs, G. J., Jr.: Am. J. Obst. & Gynec. 66, 4: 830-841, 1953.
3. Finnerty, F. A.: J. Proc. Soc. Exper. Med. & Biol., to be published.

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The American Journal of Medicine

VOL. XVI APRIL, 1954 NO. 4

Editorial

Intravascular Resistance

THE terms intravascular or "peripheral" resistance and their modifications have come into wide use and it may be of some value to analyze their meaning. Resistance is a concept to which physical values have been assigned. Thus since P is usually expressed in dynes/cm.^{2} and flow or Q in cm.^{3}/second, the ratio of pressure to flow, or P/Q, is often expressed[1] as dyne seconds/cm.^{5} This is derived from Poiseuille's law, $Q = \frac{P\pi r^4}{8l\eta}$, in which η is viscosity in dyne seconds/cm.^{2}, l is the length and r the radius of the vessel in cm. Conceptually, P/Q represents the resistance of the blood in the blood vessels to flow at any given pressure. Physically, it is determined by the vector of the frictional forces in the blood opposing the driving mean pressure. When volume flow is constant, these forces are in equilibrium and mean frictional resistance should be exactly equal to mean pressure. Resistance as P/Q, however, is this mean force in dynes *per unit* of cross sectional area and *per unit* of flow $\left(\frac{\text{dynes}}{\text{cm.}^2 \cdot \text{cm.}^3/\text{second}}\right)$. The frictional resistance in dynes is equal to the pressure in dynes/cm.^{2} multiplied by the actual mean cross sectional area, and cannot be measured unless the mean cross sectional area can be calculated. Thus transposing the above equation, $P\pi r^2 = \frac{8l\eta Q}{r^2}$. Since flow is determined both by driving pressure and cross sectional area, frictional resistance in dynes, as can be seen from the equation, is directly rather than inversely proportional to flow.[2]

In measuring intravascular resistance, as it is ordinarily done, we are therefore dealing fundamentally with a pressure-flow ratio and the accuracy of the calculation will depend upon that of the two values measured. The errors involved in measuring either systemic or regional flow need not be belabored here except to say that they are often considerable. Pressure should be true mean pressure. This is most accurately estimated when the intra-arterial pressure wave is integrated. The form and amplitude of this wave is affected by many factors including that of resonance of the elastic arterial walls. Also, venous pressure must be subtracted from mean pressure to obtain the desired pressure value. The use of arithmetic mean pressures often indirectly determined by the cuff technic and of fixed values for venous pressure introduces small but variable errors into any resistance calculation.

In addition, flow and pressure, and hence resistance, not only fluctuate within each cardiac cycle but also in response to a variety of stimuli including respiration. Such fluctuations are "smoothed out" and therefore obscured in the so-called "steady state" because the period of successive observations is considerably longer than that of the fluctuations. Fortunately the changes in mean resistance ordinarily measured are usually so large that they are apparent despite these various sources of error.

There are, however, other difficulties, especially if resistances are to be compared in the same or different individuals. The relationship between pressure and flow as measured at different levels of pressure is rectilinear or nearly so in the blood vessels, provided they are widely dilated and the blood viscosity is at or below a critical value.[3] Under these circumstances the

[1] BÖGER, A. and WEZLER, K. Die Bestimmung des arteriellen Gesamtwiderstandes am Menschen. *Arch. f. exper. Path. u. Pharmacol.*, 186: 43, 1937.

[2] MENDLOWITZ, M. Digital vascular resistance in normal, polycythemic, and hypertensive states. *Circulation*, 3: 694, 1951.

[3] WHITTAKER, S. R. F. and WINTON, F. R. The apparent viscosity of blood flowing in the isolated hindlimb of the dog, and its variation with corpuscular concentration. *J. Physiol.*, 78: 339, 1933.

straight line usually passes through or very near zero pressure and flow. Thus a single pressure-flow or flow-pressure ratio, independent of the blood pressure level, will define the angle made with the ordinate or abscissa, and if the intravascular viscosity is known, an index of the dimensions of the vascular bed perfused can be obtained. The line defining this angle, however, is obtained by dividing flow by pressure. It is the reciprocal of resistance and if viscosity is considered constant it is an index of the actual caliber or volume of the vascular bed. These conditions fulfill the requirements of Poiseuille's law and, among other things, imply that flow is viscous or laminar and not turbulent. Eddying and turbulence are known to occur in the heart and larger blood vessels, especially in pathologic states, but probably do not modify flow in the "periphery."

If the apparent viscosity of the blood in the vessels is increased, however, the relationship between pressure and flow becomes curvilinear with the convexity of the curve toward the pressure axis.[4,5] This is probably a physical phenomenon dependent on the distribution of cells and plasma in the flowing stream. It is influenced chiefly by the concentration of red cells in the blood, the concentration and characteristics of the proteins in the plasma, and also by the caliber of the vessels through which, and the velocity with which, this two-phase system flows. With decreasing vascular caliber, apparent viscosity decreases until a critical level is reached, when it increases again. Some of these changes have not, however, been clearly separated from those caused by the force of vasomotion (v. seq.). With increasing velocity, viscosity decreases until a critical level is reached, when it becomes steady. Another factor is blood temperature, which causes an inverse change in viscosity. These relationships are complex, one of the important factors being the size of the plasma "rim" of the flowing stream. Plasma is less viscous than whole blood and a greater proportion of the shearing stress in laminar flow occurs in the "rim" than in the center of the vessel. In any case, it is clear that a single flow-pressure ratio will not define the slope adequately unless the intercept on the pressure axis is known. It is better, however, to have a series of ratios at different pressure levels.

If the blood vessels are narrowed structurally or because of edema of their walls, the error produced by the change in apparent viscosity is usually small enough not to obscure major changes in caliber. If there is smooth muscle contraction, however, another complication is introduced into the measurement of resistance. Under these conditions changes in resistance or vascular volume index alone are insufficient to define the changes in vasomotor tone. For example, if the intravascular pressure or load is high, there may be less change in vascular caliber with a given stimulation than if it is low, more of the contraction being isometric, so to speak, rather than isotonic. An attempt has been made to measure this factor from the critical closing pressure, or that intra-arterial pressure at which tension in the walls of the vessels is sufficient to close them, causing cessation of flow.[6] This assumes constant smooth muscle tension, however, with decreasing pressure. In addition, the interplay between this factor and changes in apparent viscosity is not as yet clearly defined.

The problem can be met, at least theoretically, by trying to calculate the work done by vasoconstriction. Several authors, for the purpose of related calculations, have employed the device of the theoretical uniform bore single horizontal vessel with the resistance characteristics of the vascular bed under study, the diameter of this vessel being equal to the initial mean diameter of the dilated perfusing artery. A theoretical length factor, prescribed by the resistance of the vascular bed as calculated from Poiseuille's law, is assigned to such a vessel, and it is assumed that this length factor remains unchanged. This is not strictly correct since the smooth muscle of the vessels is often not circular but corkscrew-like in its arrangement so that some shortening may occur with vasoconstriction. Making these assumptions, however, one can, from pressure-flow data, calculate the change in radius of such a vessel, as produced by vasoconstriction, and then calculate the work of vasomotion.

[4] Pappenheimer, J. R. and Maes, J. P. A quantitative measure of the vasomotor tone in the hindlimb muscles of the dog. *Am. J. Physiol.*, 137: 187, 1942.

[5] Green, H. D., Lewis, R. N., Nickerson, N. D. and Heller, A. L. Blood flow, peripheral resistance and vascular tonus, with observations on the relationship between blood flow and cutaneous temperature. *Am. J. Physiol.*, 141: 518, 1944.

[6] Nichol, J., Gisling, F., Jerrard, W., Claxton, E. B. and Burton, A. C. Fundamental instability of the small blood vessels and critical closing pressures in vascular beds. *Am. J. Physiol.*, 164: 330, 1951.

Thus work in dyne cm. =

$$(r_1 - r_2)\left(\frac{P_1 + P_2}{4}\right)\left(\frac{2\pi r_1 l + 2\pi r_2 l}{2}\right)$$

or $$= \frac{\pi}{4} l\,(r_1^2 - r_2^2)(P_1 + P_2)$$

in which r_1 is the initial radius in cm., r_2 the radius in cm. after vasoconstriction, P_1 the initial mean pressure minus venous pressure and P_2 the mean pressure after vasoconstriction minus the venous pressure in dynes/cm.^{2} and l is the length of the theoretical model vessel in cm. Obviously all the means here are arithmetic assuming rectilinear regressions of r and hence of the intravascular area $2\pi rl$ and also of P, both throughout the length of the vessel and between the two phases of dilatation and constriction. These regressions are probably curvilinear and require integration for greater accuracy. Also, the calculation of r_2 from flow-pressure ratios would require correction for change in the intercept on the pressure axis as influenced by apparent viscosity as well as by critical closing pressure.

The work which can be done by any muscle, however, is directly proportional to initial length and inversely proportional to initial tension. This may be included in the formulation as follows:

$$\text{Work index} = \frac{\pi}{4} l \frac{(r_1^2 - r_2^2)(P_1 + P_2)}{r_1 \cdot \frac{P_1 - P_0}{2} \cdot \frac{2\pi r_1 l}{2}}$$

or $\dfrac{(r_1^2 - r_2^2)(P_1 + P_2)}{2r_1^2(P_1 - P_0)}$ in which P_0 is the closing pressure in dynes/cm.^{2} for any given initial caliber and pressure. This index has no dimensions and would represent that work done by vasoconstriction per unit of potential work at any initial caliber and pressure. It is to be noted that the potential work (denominator) decreases with increasing initial vascular smooth muscle contraction as measured by P_0. Again, rectilinear regressions are assumed and greater accuracy would require integration of the probably curvilinear relationships.

The complexity of the problem should be apparent from what is essentially merely a mathematical approximation. It may be asked how close to estimating the work of vasomotion one may come by measuring pressure-flow ratio or resistance changes as such. The dimensions of such a ratio, if divided by constant viscosity, is cm.$^{-3}$. Some workers have preferred vascular volume index, which is the reciprocal of resistance and has the dimensions cm.^{3}. The latter, however, is still related in a complex manner to the actual mean radius or volume of the vascular bed perfused. If the *per cent* changes in resistance are measured, however, these changes, though inverse, are similar to those for *per cent* changes in calculated vascular volume index or in calculated mean radius, despite the difference in units and in the regression curves for each of these values.[7] The factor of initial resistance as an index of initial radius, moreover, is included in such calculations. What is not included, however, is the factor of initial tension and variable load, both of which are completely disregarded. Conclusions as to the statistical significance or lack of significance of such data in hypertension or other diseases must therefore be viewed with reserve. Even if the work of vasomotion could be accurately estimated as such, the weight of such factors as initial length and initial tension as influenced by stored elastic energy as well as the energy of contraction would have to be determined. The latter would be influenced by hypertrophy of the muscle as well as by the rate of liberation of nor-epinephrine-like substances by sympathetic nerve discharge. If such discharge is blocked at the ganglia, moreover, by a fixed dose of a suitable drug, the blockade must be known to be complete in each individual before estimation of increased or decreased vasomotor tone in such states as hypertension can be made.

Nervous control of vasomotion also is complex Sympathetic nerve discharge is largely adrenergic and produces vasoconstriction. In certain parts of the body, however, there is weak dilator activity, probably cholinergic. There are at least four separate synapse levels on the motor side: in the sympathetic ganglia, the spinal cord, the hypothalamus and the cerebral cortex. Stimulatory sensory inflow can presumably come from anywhere in the body. Known inhibitory sensory inflow comes from the aorta and carotid sinus via the moderator nerves. Blockade or stimulation can be effected at any synapse level or combination of levels, as well as at the nerve endings themselves. In addition, direct blockade or stimulation of capillaries as well as of arteriolar or venular smooth muscle can be achieved. Reaction patterns are also often modified by

[7] Kowalski, H. J., Hoobler, S. W., Malton, S. D. and Lyons, R. H. Measurement of vasoconstrictor tone in the extremities in hypertension. *Circulation*, 8: 82, 1953.

reflex and direct parasympathetic effects, and for all these reasons are varied.

Although sympathetic nerve discharge seems to be the most potent factor in systemic vasoconstriction, especially in such regions as the skin, circulating substances are also known to cause vasoconstriction. Epinephrine and norepinephrine are the most familiar of these. Their effect, especially that of the latter, is similar to that produced by sympathetic nerve discharge. Serotonin, liberated from platelets as well as from other tissues, has vasoconstrictor action locally but a more complex general effect. Adrenal cortical hormones are believed to enhance the reactivity of the mechanisms responsible for vasoconstriction, and the electrolyte balance, including both sodium and potassium, may be involved in this process. Any chemical substances related to those which occur naturally will have comparable effects on vasomotor tone.

Apart from these vasomotor effects the intrinsic caliber of the vessels can be altered in various other ways. Structural changes may be produced by constriction, as in scleroderma, or by obstruction, as with arteriolar sclerosis or thrombosis. Sympathectomy may decrease intrinsic vascular caliber by causing disuse atrophy and hence shortening of the circular smooth muscle of blood vessels. It is also possible that either intra- or extracellular edema of the vessel walls due to increased concentration of electrolytes can decrease intrinsic vascular caliber. This can be influenced by many factors including the adrenal cortical hormones. Whether there is also a change in vascular muscle tone is unknown. The intrinsic resistance is also affected by changes in blood viscosity as produced by polycythemia or anemia and possibly by hypoproteinemia.

It should be evident that our knowledge of this subject is still chaotic and incomplete. It is, nevertheless, no longer sufficient to adduce changes in vascular caliber from changes in either flow or pressure alone. What is more, wherever possible, factors influencing neurogenic vasoconstriction must be separated from those affecting intrinsic vascular caliber. It must never be forgotten that what happens in the "peripheral" circulation influences the cardiovascular system as a whole, especially in such diseases as hypertension. Despite its complexity, therefore, we must continue to address ourselves to the understanding of intravascular resistance and continue to apply established physical and physiologic principles to the solution of the problems raised by such studies.

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Clinical Studies

Studies on the Mechanism of Ventricular Activity*

VI. The Depolarization Complex in Pure Subendocardial Infarction; Role of the Subendocardial Region in the Normal Electrocardiogram

MYRON PRINZMETAL, M.D., CLINTON McK. SHAW, JR., M.D., MORTON H. MAXWELL, M.D., EILEEN J. FLAMM, ALFRED GOLDMAN, M.D., NOBORU KIMURA, M.D., LOUIS RAKITA, M.D., JEAN-LOUIS BORDUAS, M.D., SOL ROTHMAN, PH.D. *and* REXFORD KENNAMER, M.D.

Los Angeles, California

According to prevailing theory, depolarization of the ventricular wall proceeds uniformly from endocardium to epicardium as an advance of dipoles.[1] Activation of the subendocardial layers thus is presumed to cause the initial portion of the normal R wave in surface and precordial leads. Conversely, inactivation of the deeper myocardium, as in subendocardial infarction, presumably results in the occurrence of an abnormal initial Q. Experimental evidence supporting this theory has been obtained by Wilson and his associates from their analysis of a chronic infarct produced by coronary artery occlusion in the dog.[2d] Histologic examination of the heart revealed a cone-shaped lesion consisting of through and through muscle death in the center and broad regions of subendocardial infarction at the periphery. Surface leads registered over the transmural portions exhibited QS deflections while the subendocardial extensions yielded surface QR or notched QS waves. As interpreted by Wilson and subsequent workers, the abnormal Q deflections resulted from transmission of negative cavity potentials through dead muscle to the surface. A positive potential presumably was then contributed by intact subepicardial muscle, causing a small R wave following the Q.

Although Wilson's classic experiment apparently has not been repeated, almost all workers concur with his conclusion that subendocardial infarcts yield abnormal QR or notched QS waves. The general acceptance of this conclusion thus must be due not to adequate direct evidence but rather to its consistency with prevailing electrophysiologic theory concerning the manner of ventricular depolarization. Recent observations in the normal dog heart, however, clearly indicate that activation of the ventricles is a much more complicated process than originally supposed.[3,4] These observations, together with the availability of improved electrocardiographic methods, prompted the present investigation of the depolarization complex associated with subendocardial infarcts. Included in the study are seven pure subendocardial lesions encountered among a series of sixty-eight chronic infarcts produced in dogs by coronary artery ligation. In addition, twelve instances of acute subendocardial damage inflicted with an electric cautery have been observed. Electrocardiographic findings in the chronic and acute subendocardial lesions are described in Part I of the present report. Part II concerns pertinent observations on depolarization in normal hearts as recorded on a Sanborn Twin-Beam electrocardiograph and a cathode-ray oscillograph.

PART I: SUBENDOCARDIAL INFARCTION

Review of the Literature

Experimental Studies. In 1934 Wilson and coworkers provided an experimental basis for

* From the Institute for Medical Research, Cedars of Lebanon Hospital, and the Department of Medicine, University of California School of Medicine, Los Angeles, Calif. Aided by grants from the United States Public Health Service and the L. D. Beaumont Trust Fund. Read before the American College of Chest Physicians, California Chapter, December 2, 1951; the Western Society for Clinical Research, January, 1952; the Society for Experimental Biology and Medicine, February 7, 1952; the Boston City Hospital, May 9, 1952.

electrocardiographic theory by recording the QRS changes associated with chronic myocardial infarction in dogs.[2] Contrary to present practice these electrocardiographers connected their apparatus so that positive potentials were registered as downward deflections (Q or S waves) while negative potentials yielded upright deflections (R waves). From an examination of direct epicardial leads recorded in this manner, they concluded: " . . . where the inner layers of muscle are dead or have been replaced by scar tissue and where the outer layers are still living and responding to the excitatory process, the QRS group is characterized by the presence of both an abnormally large initial summit and a conspicuous intrinsic upstroke. A pronounced downward movement usually separates these two deflections but may be absent."[2d] Thus according to Wilson, the surface over pure subendocardial infarcts or over the subendocardial edges of cone-shaped transmural infarcts would present QR or notched QS waves in leads connected by the method now in use.

Subsequent studies of experimental subendocardial lesions in animals were designed primarily to determine the direction and extent of RS-T segment deviation during acute stages of the lesion. Although QRS changes were noted only incidentally or not at all, a number of observations are worthy of note. Kisch, Nahum and Hoff[5] injected M/5 potassium chloride into the subendocardial region of the left ventricle in dogs, cats and rabbits. Standard limb leads recorded after the chest was closed and the lungs re-expanded failed to show abnormal QRS complexes. Boyd and Scherf[6] likewise observed no striking modification in the standard leads after scarifying the inner surface of the left ventricular apex in seventeen dogs. Pruitt, Barnes and Essex[7] obtained no QRS alterations in standard leads after subendocardial trauma was inflicted by applying traction to a coiled piano wire inserted into the apex of the dog's ventricle. In lead IVR, however, the normal R wave became smaller following traumatization of the wall in sixteen of twenty-two animals and the S wave deepened in ten. The remaining six instances, none of which had presented a Q wave in control tracings, yielded an initial downward deflection or notch on the upstroke of the R wave in IVR after subendocardial injury. An increase in the width of the QRS complex was found in only two of twenty-two lesions, both involving muscle high on the interventricular septum. Wolferth, Bellet, Livezey and Murphy[8] recorded direct surface leads after injection of potassium chloride into the subendocardial region in dogs. Although the effect of this procedure on the QRS complex was not discussed, the many tracings published by the authors consistently failed to show Q waves. Hellerstein and Katz[9] found Q waves in direct epicardial leads only over complete transmural injuries in the dog's ventricle but noted a minimal decrease in the amplitude of the R and S waves over subendocardial lesions. Pruitt and Valencia[10] analyzed RS-T segment changes in direct leads over subendocardial burns in the turtle's heart. Of the two tracings reproduced in their report one exhibited a small Q wave while the other contained an apparently normal QRS complex.

Clinicopathologic Studies. A review of clinicopathologic reports during the past decade reveals conflicting results concerning the electrocardiogram of subendocardial infarction in man. Pardee and Goldenberg[11] correlated the pathologic findings in eleven infarcts with QRS changes in three standard leads and IVF. Although four of the eleven lesions were described as subendocardial, only one failed to involve epicardial muscle in some part of the heart. An initial Q wave occasionally was registered in precordial leads directly over the region of subendocardial infarction but limb leads in these instances seldom presented patterns typical of anterior or posterior infarcts. Subendocardial lesions in the anterior wall yielded records similar to those seen after exercise and anoxemia tests and during anginal attacks.

In an extensive study by Myers and co-workers[12] multiple precordial and limb leads from 161 patients with myocardial infarction were related to the pathologic findings observed at autopsy. Six of the cases presented anteroseptal infarctions involving the subendocardial one-half to two-thirds of the wall. An initial Q wave was found in at least one precordial lead from each of these six cases. Of nineteen infarcts affecting the innermost one-fourth to three-fourths of the anterolateral wall, eleven yielded abnormal QR waves or coarsely notched QS waves in V_3 and V_4; four presented smooth or slightly notched QS waves; the remaining four exhibited an initial R wave in V_3 and V_4. Leads V_5 and V_6 showed QR waves in twenty-six of thirty-three infarcts involving the subendocardial one-fourth to three-fourths of the lateral wall. Although the authors did not explicitly distinguish pure

subendocardial infarcts from subendocardial extensions of transmural infarcts, histologic descriptions of the entire lesion were presented in each case. An analysis of these descriptions revealed that variable amounts of surface involvement occurred in at least 154 instances. Whether or not the remaining seven infarcts were purely subendocardial could not be determined from the reported data.

A subsequent report by Myers, Sears and Hiratzka[13] describes fifteen cases of extensive ring-like subendocardial infarcts. QR waves were obtained in eight of the fifteen cases, while tracings diagnostic of septal infarction were registered in one case, left bundle branch block patterns were recorded in five cases and a normal QRS complex appeared in one case. Levine and Ford,[14] unlike Myers, consistently failed to obtain Q waves in precordial leads from their six cases of ring-like subendocardial infarction.

In addition to the larger series reviewed above, the literature contains numerous case reports concerning one or two instances of anterior subendocardial infarction. Lepeschkin[15] lists ten reports in which the authors state that no pathologic Q waves occurred in precordial tracings over subendocardial infarcts, as well as four reports of similar lesions which presented an initial Q wave in at least one lead.

The preceding review of medical literature clearly fails to provide definitive evidence concerning the depolarization complex associated with subendocardial infarction. Both experimentally and clinically, pathologic Q waves were registered in some instances but not in others. Such conflicting results are scarcely surprising in view of the marked differences in genesis, age and extent of the lesions studied. All experimental subendocardial infarcts except Wilson's were produced by direct traumatization with relatively crude methods. The clinical infarcts, on the other hand, presumably resulted from coronary occlusion or other mechanisms causing reduced blood supply to the heart. Again with the exception of Wilson's case, all the experimentally produced lesions were acute; that is, they were observed within a few hours after onset, before pathologic and electrocardiographic changes could be fully developed. The clinical infarcts studied, in contrast, ranged in age from a few hours or days to several years. Finally, perhaps a serious limitation of both experimental and clinical studies was the failure to distinguish between pure subendocardial infarcts and infarcts which are largely subendocardial but involve some muscle in the outer ventricular layers.

Materials and Methods

The present study of subendocardial infarction was designed to control the three factors assumed to be responsible for inconsistencies in previously reported results. First, chronic lesions were produced by a mechanism comparable to that occurring in spontaneous myocardial infarction in man. Second, a series of acute lesions was produced and the electrocardiographic changes compared with those obtained over chronic infarcts. Third, if transmural involvement was present in any part of the heart the infarct was excluded from the study. Only pure subendocardial lesions are reported.

Chronic Infarcts. In each of sixty-eight dogs the left anterior descending coronary artery was ligated about halfway down its course. Myocardial changes were allowed to develop over periods ranging from two days to five months and averaging forty-two days. Routine limb and precordial tracings were then made. The chest was reopened and the heart widely exposed.

Direct electrocardiographic exploration of the infarcted ventricle included epicardial, intramural and cavity leads from multiple sites. The recording equipment and technic were the same as those used in a previously reported investigation of the normal dog heart.[3b] Intramural and cavity tracings were recorded from a specially designed plunge electrode the diameter of a fine needle. As demonstrated by a series of tests these electrodes register essentially local potentials in accordance with Poisson's law. Epicardial leads were made with a small cotton-tipped electrode soaked in warm saline.

Upon completion of the electrocardiographic exploration the heart was removed with the plunge electrodes *in situ*. Tissue in and around the infarcted region was cut and immediately placed in formaldehyde. After the tissue had been fixed sections were prepared for histologic study. Each section was stained with a connective tissue stain which clearly differentiated fibrotic from normal muscle. Hematoxylin and eosin stain was also used to distinguish between intermediate grades of pathology. The sections were then viewed microscopically and drawings made to show the distribution of the lesion. In all instances the slides were examined "blind"; that is, the observer was ignorant of the electro-

cardiographic appearance of the section. The histologic findings were confirmed by at least two independent observers.

The path made by the plunge electrode often was clearly visible in microscopic views of the stained section, appearing as a narrow tract in the myocardium. Since all intramural leads had been registered at known distances from the ventricular surface, it was possible to identify the approximate site on the tract from which each tracing was derived. The various epicardial, intramural and cavity complexes recorded during the experiment were pasted on drawings or enlarged microphotographs of the sections at locations corresponding to their sites of origin. Thus the electrocardiographic and pathologic changes in the infarcted ventricle could be closely correlated.

Acute Lesions. In eighteen animals an attempt was made to produce acute subendocardial lesions by electrocoagulation. Surface leads from various sites on the left ventricle were recorded at the beginning of each experiment. Control tracings from intramural levels also were obtained in several instances. A cautery was then inserted into the left auricular appendix through a purse-string suture, passed through the mitral valve into the left ventricular cavity, and placed in contact with various sites on the endocardium. After burns had been inflicted, the epicardial surface was again explored electrocardiographically.

As observed by other workers,[5,9,10] the production of purely subendocardial burns was extremely difficult. In several instances necrotic tissue was observed at all levels of the wall from endocardium to epicardium. In other animals the only pathologic changes consisted of localized hemorrhage or pallor near the endocardial surface with little or no penetration. Twelve of the eighteen burns were considered satisfactory examples of pure subendocardial necrosis. These twelve lesions began at the endocardium and extended through from one-eighth to four-fifths of the thickness of the wall.

Results

Chronic Subendocardial Infarcts. Of the sixty-eight chronic infarcts produced by coronary artery ligation, seven involved only subendocardial muscle. (Table I.) These pure subendocardial infarcts were studied from fourteen to seventy-seven days after the artery was tied. They varied in size from minute areas of fibrosis at and immediately above the endocardium (Case C16) to extensive lesions involving more than one-half the thickness of the ventricular wall (Case C15). The outermost ventricular layers from base to apex consistently appeared within normal limits on gross inspection. Thus no evidence of infarction was visible with the heart *in situ*. (Fig. 1A.) Only after the ventricle had been removed and sectioned was the presence of the lesion established. (Fig. 1B.)

TABLE I

ANALYSIS OF THE DEPOLARIZATION COMPLEX IN DIRECT EPICARDIAL LEADS FROM SEVEN INSTANCES OF CHRONIC SUBENDOCARDIAL INFARCTION PRODUCED BY CORONARY ARTERY LIGATION IN DOGS

Exp. No.	Days after Ligation	Extent of Wall Involved	Amplitude of QRS (mm.)		
			Q	R	S
C2	14	Inner one-third	0.0	11.5	7.0
C13	24	Inner one-fourth	0.5	11.0	5.0
C15	26	Inner one-third	0.0	19.0	0.0
		Inner two-thirds	0.0	8.5	3.0
C16	26	Inner one-eighth	0.0	5.0	4.0
C18	49	Inner one-half	0.0	1.0	15.0
C23	77	Inner one-third	0.0	16.0	7.0
C34	24	Inner one-fourth	0.5	16.0	5.0

Histologic study confirmed the presence of dead subendocardial tissue underlying intact subepicardial muscle in five cases. The remaining two instances presented some pyknotic nuclei and loss of striae in the epicardial region. Since a similar histologic picture has been seen in normal hearts,[16] these minor changes were attributed to exposure of the surface and were not considered as extensions of the infarct.

Standard limb leads from six of the seven animals with pure subendocardial infarcts were essentially normal. (Fig. 2.) The exception consisted of Case C13 which presented RS-T segment elevation and abnormal T waves in leads I and II. Multiple precordial tracings also were normal in all but one animal (Case C34) which yielded inverted T waves and elevated RS-T segments of "coronary" configuration from some precordial points. In no instance was a QR or QS wave present in the limb or precordial leads. The width as well as the shape of the QRS complexes was within normal limits.

Epicardial leads from various sites over the

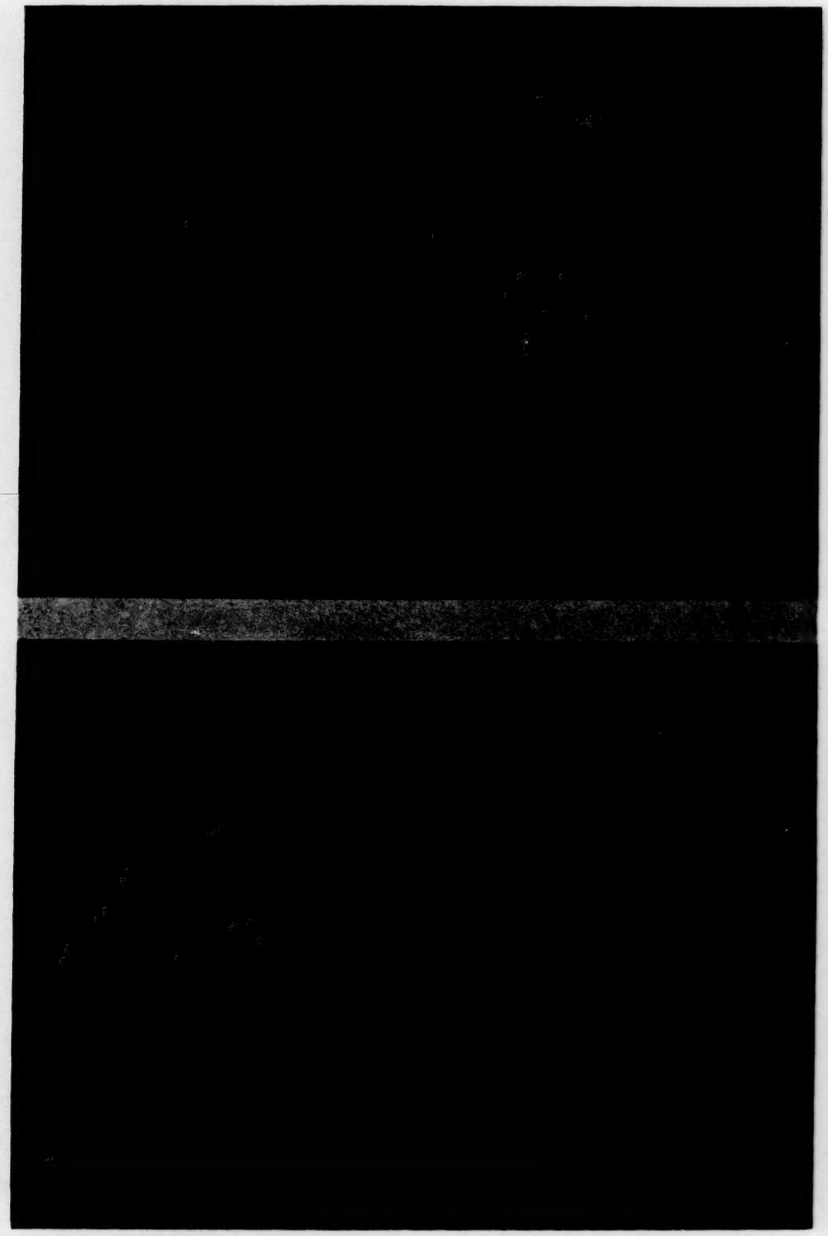


FIG. 1. Photographs of heart with chronic subendocardial infarct. A, intact heart, anterior view. The ventricular surface appears normal except for localized area of pericarditis over the ligature (L) at the proximal segment of anterior descending coronary artery. B, sagit al section. A circumscribed subendocardial infarct involving the inner one-half of the anterolateral wall of the left ventricle can be seen.

subendocardial infarcts likewise consistently failed to contain abnormal Q waves. (Figs. 3 to 6.) In six instances the surface deflections were indistinguishable from those registered over normal hearts. The remaining lesion (Case C18) yielded small R waves probably lower than those in control leads. Intramural tracings recorded over and within the infarcted regions appeared normal. (Fig. 6.)

Acute Subendocardial Lesions. Grossly and histologically, the twelve subendocardial lesions produced by electrocoagulation presented variable amounts of myocardial change. In some instances the only pathologic finding consisted of

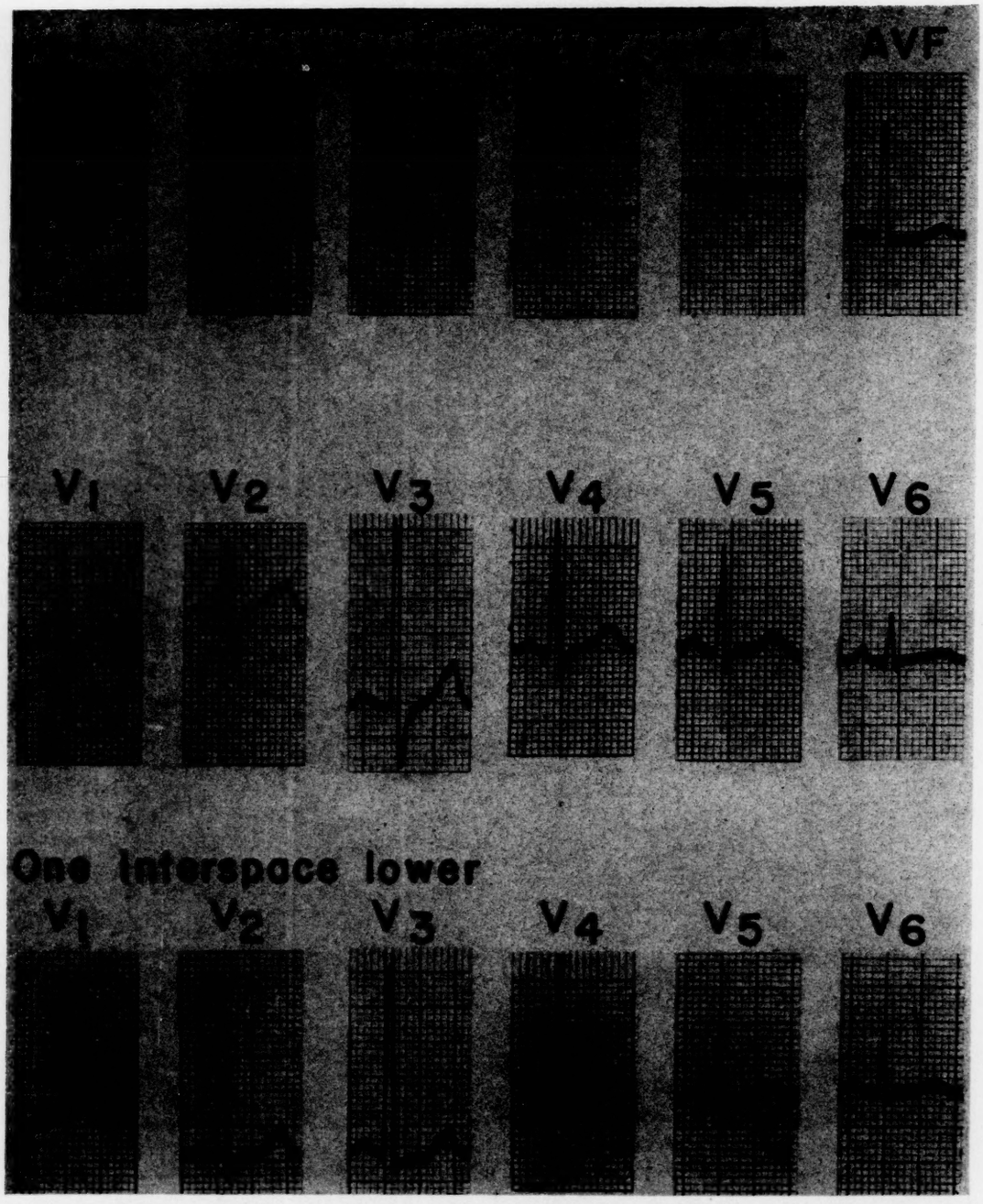


FIG. 2. Standard limb and precordial leads from dog with subendocardial infarct studied forty-nine days after coronary artery ligation (experiment C18). Tracings registered at paper speed of 50 mm. per second, attenuation × 1. Sensitivity: 1 mv. = 1 cm. The width, amplitude and configuration of the QRS complexes are similar to those recorded from dogs with normal hearts. No abnormal Q waves are present in precordial leads over the subendocardial infarct. The S-T segments and T waves are probably within normal limits.

pallor or slight hemorrhage at the endocardium. (Table II, Cases A5, 6 and 7.) In other cases necrosis involved all but the outermost layers of the wall (Cases A3, 4 and 9). Surface leads made before the endocardium was burned exhibited large R waves usually followed by a relatively small S component. Tiny Q waves, probably within normal limits, preceded the R wave in two records (Cases A1 and 2). These control tracings were compared with leads

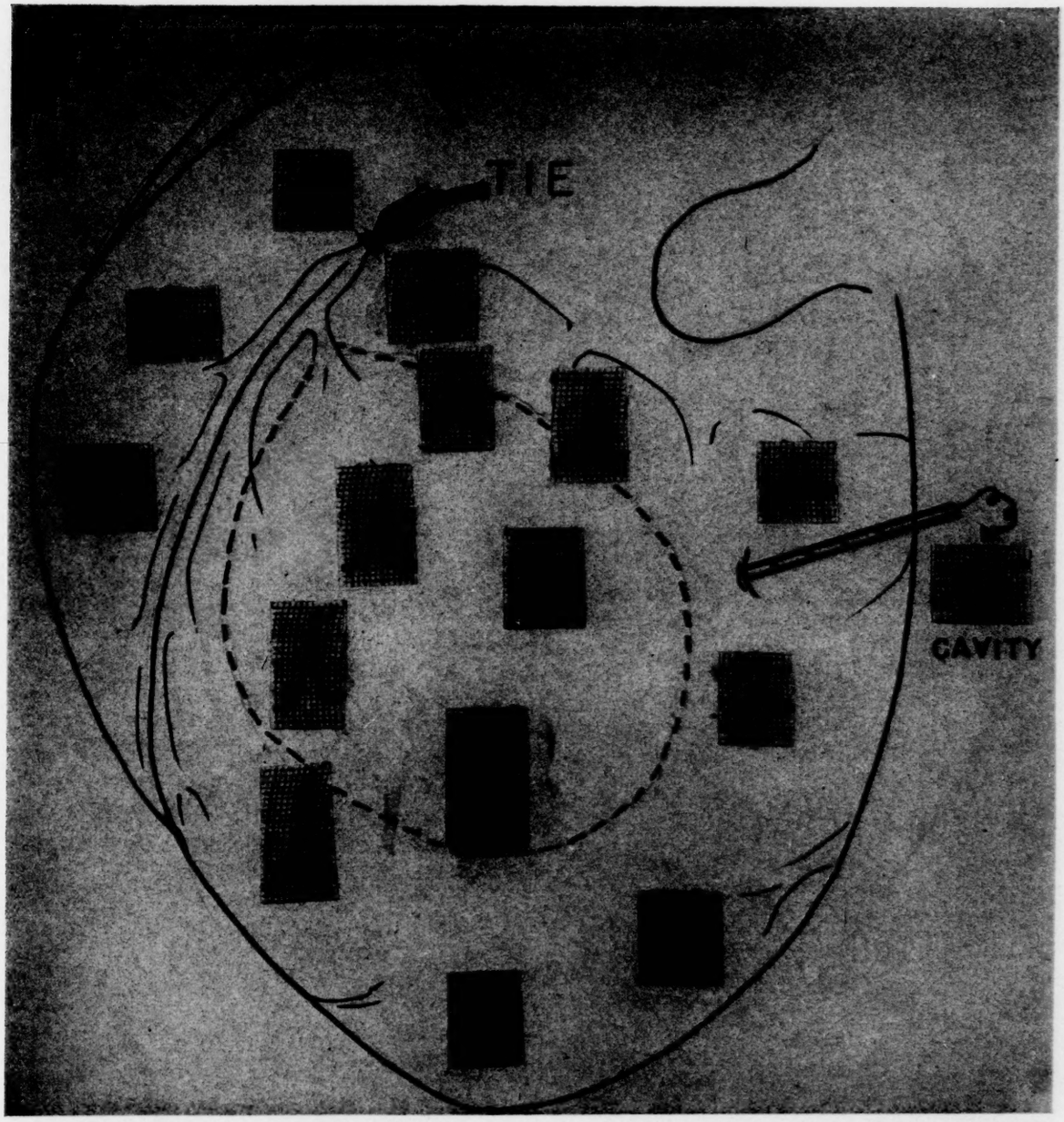


FIG. 3. Direct epicardial and cavity leads from left ventricle recorded twenty-six days after coronary artery ligation (experiment C15). Tracings registered at paper speed of 125 mm. per second, attenuation × 20; 20 mv. = 15 mm. Histologic examination showed subendocardial infarct involving inner one-third of wall directly beneath area indicated by dotted line. All surface complexes consist of normal r or Rs waves; no Q waves were observed over infarct. Cavity yields a pure QS wave.

recorded directly over the damaged areas from three to thirty minutes after the burns were inflicted. As shown in column 5 of Table II, a lowering of the R wave was seen in ten of the twelve instances. In two experiments (Cases A8 and 11) the height of the R waves remained essentially unchanged. No apparent relationship existed between the percentile decline of the R wave and the extent of the lesion. For example, a small endocardial hemorrhage reduced the R wave to half its original height (Case A5) whereas a large lesion involving the inner two-thirds of the wall caused only slight lowering of the deflection (Case A1). Surface leads not directly over the subendocardial lesions usually presented normal R or Rs waves.

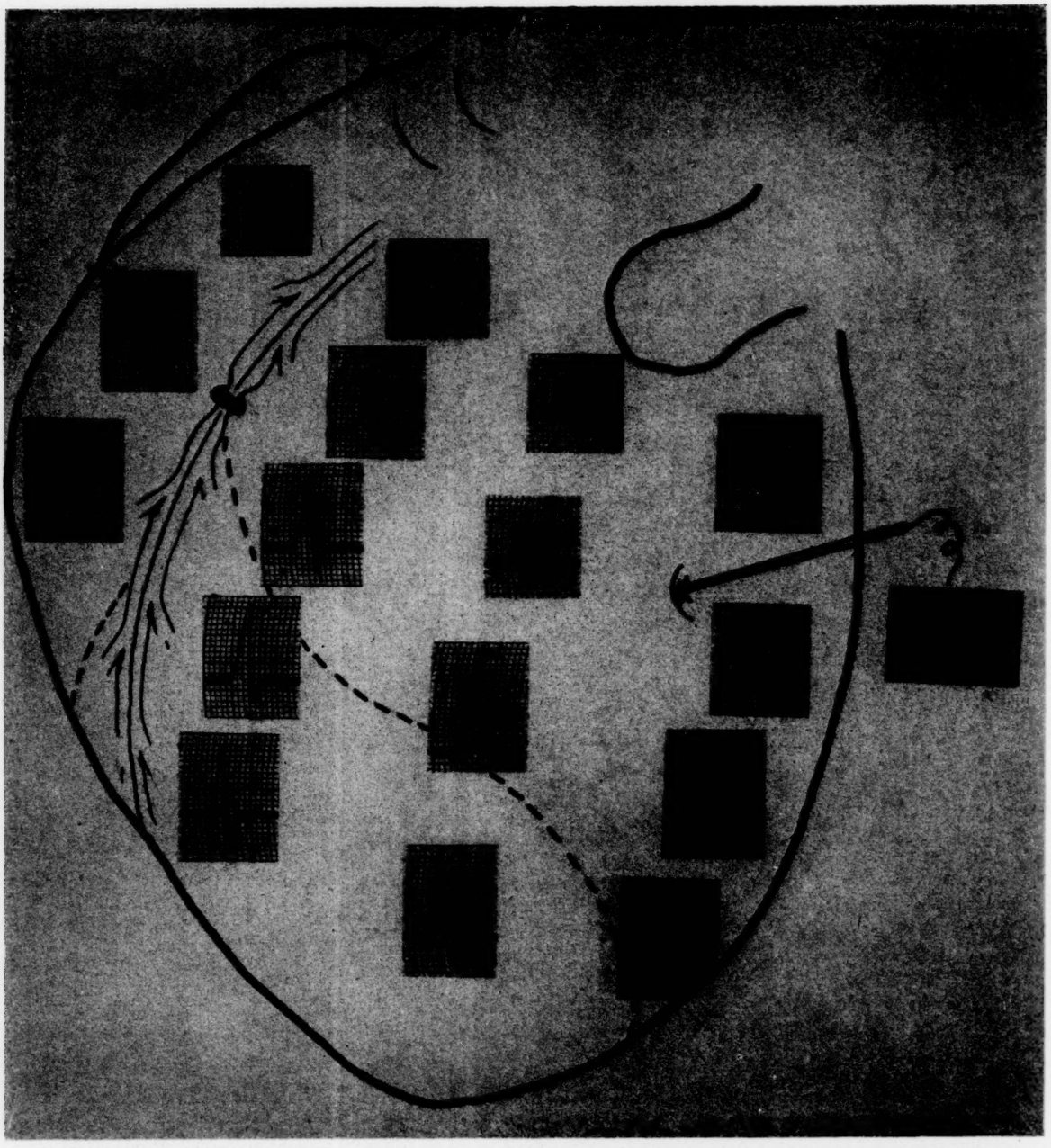


FIG. 4. Direct epicardial and cavity leads from left ventricle twenty-four days after coronary artery ligation (experiment C34). A subendocardial infarct involving inner one-fourth of anterior wall and apex was present in this instance. The surface over the infarct, shown by dotted line, yielded normal Rs waves.

The small Q waves observed in control tracings from two animals were deeper and broader after subendocardial burns were inflicted. This growth of the Q wave was absolute as well as relative to the size of the R wave. None of the remaining ten subendocardial lesions yielded evidence of a Q wave in surface leads.

PART II: ROLE OF SUBENDOCARDIAL MUSCLE IN THE NORMAL ELECTROCARDIOGRAM

The subendocardial infarcts described in Part I consistently failed to yield abnormal initial Q waves. Surface and precordial leads registered over the chronic lesions presented normal R and Rs waves. It is thus evident

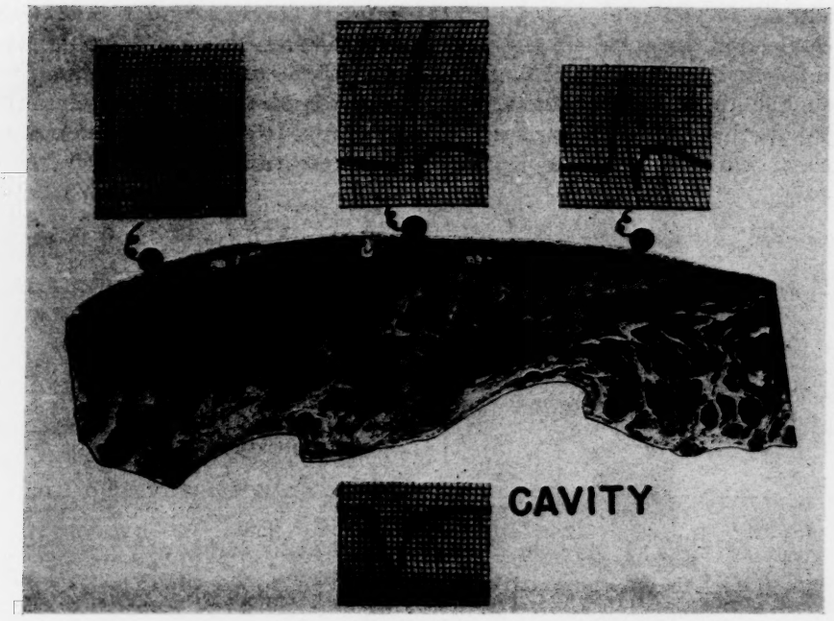


FIG. 5. Electrocardiographic and histologic appearance of section of left ventricle seventy-seven days after coronary artery ligation (experiment C23). Fibrous tissue appears white or grayish-white, surviving muscle dark gray or black. A subendocardial infarct involves the inner one-third of the wall. Surface complexes over the lesion are predomi antly positive and within normal limits.

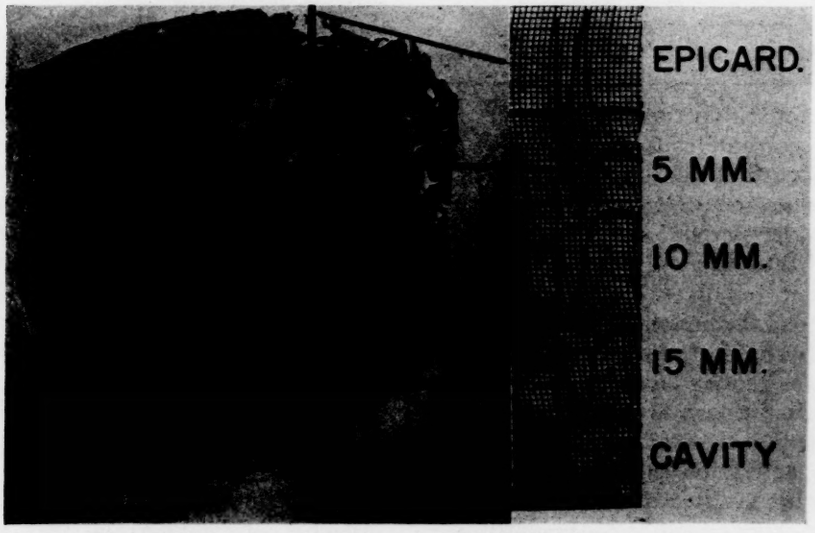


FIG. 6. Epicardial, intramural and cavity leads from left ventricle recorded twenty-six days after coronary artery ligation (experiment C15). Photomicrograph shows subendocardial infarct involving inner one-thi :d of wall. Heavy black line represents approximate path of plunge electrode; magnification × 13. The surface complex consists of a normal R wave. Intramural QS deflections are similar to those recorded from normal hearts.

that the subendocardial region has little or no effect on the depolarization complex. For practical purposes, therefore, subendocardial depolarization may be considered "electrocardiographically silent"; that is, it does not contribute to the electrocardiogram. This observation appears to conflict with classic electrocardiographic theory concerning both normal and abnormal hearts. First, subendocardial depolarization is supposed to generate the initial part of

the positive potential (R wave) recorded over normal ventricles. Second, as noted previously, subendocardial infarcts should yield QR waves. In order to reconcile these conflicts between theory and actual findings, the depolarization process in the normal ventricle must be reviewed.

present purely negative potentials (QS waves). All intramural muscle would face the positive side of the dipole at the onset of depolarization and would therefore exhibit an initial positive potential (R wave). All levels of the wall except the epicardium would face the negative pole

TABLE II

ANALYSIS OF THE DEPOLARIZATION COMPLEX IN DIRECT EPICARDIAL LEADS FROM TWELVE INSTANCES OF ACUTE SUBENDOCARDIAL BURNS IN DOGS

(1) Exp. No.	(2) Minutes after Burn	(3) Extent of Wall Involved	(4) Amplitude of Q (mm.)		(5) Amplitude of R		
			Control	After Burn	Control (mm.)	After Burn (mm.)	Change (%)
A1	4	Inner two-thirds	0.5	2.0	9	7	−22
A2	4	Inner one-third	0.5	2.0	23	19	−17
A3	25	Almost transmural	0.0	0.0	16	9	−44
A4	13	Almost transmural	0.0	0.0	19	10	−47
A5	25	Endocardial hemorrhage	0.0	0.0	18	9	−50
A6	3	Endocardial hemorrhage	0.0	0.0	6	4	−33
A7	10	Endocardial hemorrhage	0.0	0.0	18	14	−22
A8	3	Endocardial pallor	0.0	0.0	21	22	+ 5
A9	20	Almost transmural	0.0	0.0	12.5	7	−44
A10	7	Inner one-fourth	0.0	0.0	12	10	−17
A11	30	Inner one-fifth	0.0	0.0	17	17	0
A12	20	Inner one-half	0.0	0.0	17.5	8	−54

It should be noted that the S-T segments and T waves in precordial leads directly over the chronic subendocardial infarcts were normal in six of the seven instances observed. Repolarization as well as depolarization of the subendocardial layers thus may be "electrocardiographically silent." This subject, however, is beyond the scope of the present paper and will be discussed elsewhere. The following observations concern only the genesis of the depolarization (QRS) complex in the normal electrocardiogram.

According to the classic concept of cardiac depolarization, activation of the normal ventricular wall occurs as a steady, constant advance of dipoles from endocardium to epicardium.[1] The positive pole precedes the negative pole, while the boundary between the poles corresponds to the activation front. If this concept is valid, the intramural potentials resulting from activation of the wall should be distributed so that half the muscle is predominantly positive and half is predominantly negative. Only the ventricular cavity and endothelium would face the negative side of the dipole throughout depolarization. Consequently, only they should

at the end of depolarization and would therefore show a final negative potential (S wave). Intramural muscle near the endocardium would yield a small R wave followed by a large S wave, as it is activated early in the depolarization period. Muscle equidistant from the endocardium and epicardium would present R and S waves of equal size, as it is activated halfway through depolarization. Muscle more distant from the endocardium would exhibit a relatively large R wave and a small S wave, as it is activated late. The R wave recorded from the epicardial surface would begin with activation of the endocardium and would end with an intrinsic deflection as the activation front reached the electrode. All levels of the wall, including the subendocardial region, thus would contribute to the R wave recorded over normal hearts.

If subendocardial depolarization contributed to the normal electrocardiogram, subendocardial infarction should yield abnormal depolarization complexes; namely, QR waves. The preceding theory of ventricular activation must therefore be modified in order to explain why normal R or

Rs waves occurred over the subendocardial infarcts discussed in Part I. Such an explanation is suggested by intramural studies of the normal dog ventricle.[3] During the last three years, leads from several thousand sites at various levels of the ventricular wall have been recorded in over 200 animals. Despite the great technical difficulties involved in these studies, two significant observations repeatedly were made:

1. Contrary to classic theory, all intramural levels of the ventricular wall did not yield initial R waves. Intramural leads from the inner layers presented pure QS waves. (Figs. 7, 8 and 10.) As the electrode was moved from endocardium to epicardium a small initial r wave usually first appeared near mid-ventricular levels. The r wave slowly and irregularly increased in width and amplitude until the electrode was within a few millimeters of the epicardial surface. A much more rapid growth of the positive deflection then occurred as the superficial levels were traversed. Tracings registered directly beneath the epicardium presented R or Rs waves almost identical with the epicardial complex.

2. The preceding results were obtained in all regions of the left ventricular wall from base to apex. Although the complexes recorded from a given level varied somewhat in different hearts and in different parts of the same heart, the inner third of the wall generally yielded pure negative depolarization waves. The middle third presented deep negative deflections usually preceded by small r waves. Only the outer third showed relatively large positive deflections. Thus the negative depolarization potentials in the normal left ventricular wall considerably exceeded the positive potentials. The right ventricle, the septum and the papillary muscle also exhibited predominantly negative depolarization potentials.

Since these observations conflict with theory concerning the manner of ventricular depolarization, the experimental methods were subjected to prolonged critical examination. Several months and over fifty experiments were devoted to intensive search for possible sources of technical error. Particular attention was given in especially designed experiments to the following seven factors which may have affected the tracings:

1. Recording Range of Intramural Electrode. Poisson's formula[17] specifies that the "potential of a given dipole as determined at a certain point within its electromotive field will vary in inverse relationship to the second power (for a volume conductor of infinite size) or to the third power (for a volume conductor of finite size) of the distance of this point from the center of the dipole." By placing a small electrode within the intramural myocardium it should therefore be possible to record relatively local potential variations at the lead-point resulting from activation of the surrounding wall. This principle constitutes the theoretic basis for the intramural recording technic used in the present study. A plunge electrode with an extremely small recording surface was employed and tracings were attenuated to $\frac{1}{20}$ of standard size in order to record essentially local potentials. As described elsewhere,[3b] several experimental procedures were devised to determine the extent to which potentials of muscle distant from the electrode affected the intramural tracings.

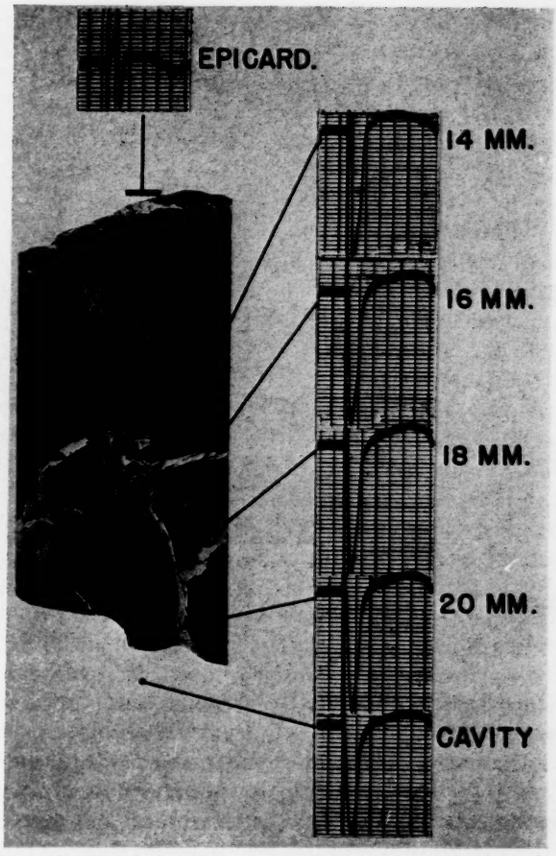


FIG. 7. Unipolar epicardial, intramural and cavity leads from normal left ventricle. Tracings recorded on Sanborn Twinbeam electrocardiograph at paper speed of 75 mm. per second. Intramural leads registered 14, 16, 18 and 20 mm. below surface present pure QS waves identical with cavity complex. Absence of initial R wave suggests that these levels of the wall depolarize too rapidly to affect the electrocardiogram.

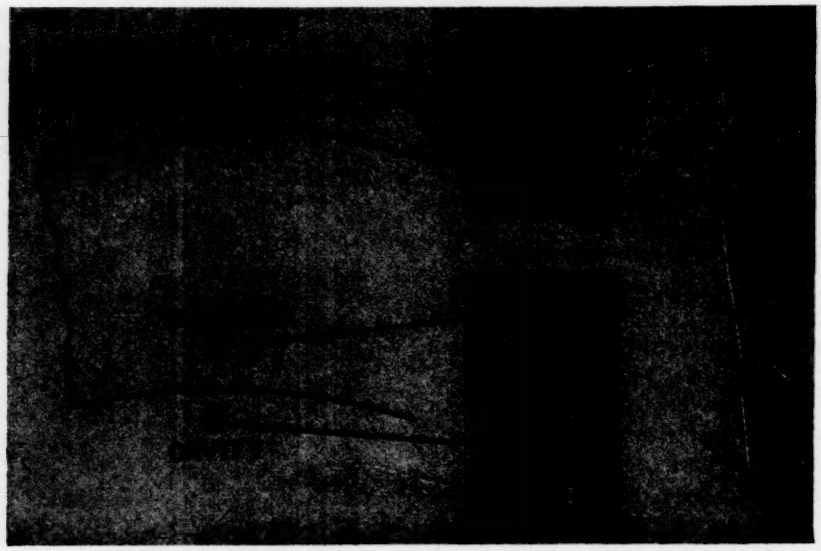


FIG. 8. Unipolar leads from various levels of normal left ventricle. Tracings from cavity and subendocardial region present identical QS waves. Subepicardial region yields an Rs wave similar to the epicardial complex. Note that epicardial and subepicardial R waves begin simultaneously with subendocardial and cavity QS waves.

The results consistently showed that the tracings represented potential variations of a highly localized region around the lead-point and were influenced relatively little by potentials of more distant areas. Thus the predominantly negative depolarization complexes registered from the normal ventricle could not be attributed to the effects of distal potentials.

2. Open Chest. Experiments were routinely performed with the chest open. The question was raised whether exposure of the ventricle could induce abnormalities in the depolarization complex. Two alternative technics were therefore employed in a number of animals. In some instances the chest was opened, plunge electrodes sutured in place at intramural levels and tracings made. The lungs were then inflated and the chest closed, after which a second set of tracings was recorded. In other instances the abdomen was opened and a plunge electrode inserted through the diaphragm into the ventricular wall without opening the chest. Tracings obtained through the closed chest by these two methods were compared with records from the exposed ventricle. Although some differences in the depolarization complex were noted, the subendocardial leads always presented pure QS waves. Whether the chest was open or closed, purely or predominantly negative depolarization complexes were recorded from all but the outermost ventricular layers.

3. Wilson's Central Terminal. Unipolar intramural leads usually were recorded with the exploring electrode at the intramural lead-point and the indifferent electrode connected to Wilson's central terminal. In view of the abnormal conditions of the experiment, it was thought that Wilson's central terminal might not be at or near zero potential. Under such circumstances the records of intramural potentials could show significant distortion. In several experiments, therefore, the indifferent electrode was moved from Wilson's central terminal to the left foot. The left foot is so distant from the heart that its potentials should be negligible as compared with those at an intramural lead-point. Tracings recorded with one electrode in the ventricle and the other on the left foot thus would provide an accurate representation of the intramural potential. These tracings exhibited predominantly negative depolarization complexes similar to those obtained when the indifferent electrode was at Wilson's central terminal. Any distortion of the intramural tracings resulting from the use of Wilson's central terminal with the chest open thus was shown to be insignificant.

4. Electrode-induced Changes in Depolarization. If the presence of the plunge electrode in the myocardium significantly altered the depolarization process, accurate records of normal intramural potentials could not be made. This problem was minimized by employing an elec-

trode of extremely small diameter and inserting it into the ventricle with great care. Nevertheless, special experiments were considered necessary to establish that focal block or other electrode-induced abnormalities did not distort the depolarization complex. In several animals an epicardial lead was recorded simultaneously with an intramural lead from subepicardial muscle directly beneath the epicardial lead-point. The depolarization complexes in the two leads were identical in width and markedly similar or identical in configuration. Simultaneous leads from the ventricular cavity and from subendocardial muscle within a few millimeters of the cavity lead-point also presented similar or identical depolarization complexes. It is generally agreed that epicardial and cavity leads are free from electrode-induced artefacts. Hence the epicardial and cavity complexes recorded in these experiments presumably were normal. On the other hand, if the intramural electrode significantly altered local depolarization the subepicardial and subendocardial complexes would be distorted. Actually, similar or identical complexes occurred in the subepicardial and epicardial leads. The subepicardial complex as well as the epicardial complex must therefore be essentially normal. Likewise, the similarity of the subendocardial and cavity complexes indicates that the subendocardial electrode did not record significant artefacts.

5. Electrodes and Insulation. Almost all intramural tracings were recorded with electrodes made of insulated tempered silver wire 10 to 20 mils in diameter. The recording surface of the electrode was coated with silver chloride. During later stages of the study tungsten wire and platinum wire in sizes ranging from 5 to 20 mils were tested. Several insulating materials also were used; these included baked varnish, enamel, synthetic lacquer and formvar. The complexes recorded with different electrodes were essentially similar regardless of the type of wire or insulation employed. All electrodes which did not present obvious technical defects registered purely negative depolarization complexes throughout the inner ventricular layers and a predominance of negativity over positivity in both ventricles, the septum and the papillary muscles.

6. Recording Apparatus. Four types of recording apparatus were used during the present study: A two-channel Brush recorder; a four-channel direct-writing Sanborn Polyviso electrocardiograph; a photographic-writing Sanborn Twin-Beam electrocardiograph with a maximum accurate frequency response of 500 cycles per second, and two DuMont dual-beam cathode-ray oscillographs (types 279 and 322A) with frequency response up to 30,000 cycles per second. A Fairchild Oscillo-Record camera (type 314A) and two Grass Pre-Amplifiers (P4) were used with the oscillographs. These four types of equipment differ considerably with respect to sensitivity. They did not, however, yield different conclusions concerning the distribution of intramural depolarization potentials. As compared with tracings recorded on the electrocardiographs, intramural leads registered on the oscillographs often exhibited tiny initial r waves at somewhat deeper levels. The inner ventricular layers nevertheless presented pure QS waves in the oscillograms as well as in the electrocardiograms.

Regardless of the many variations in recording methods and the many types of equipment employed, the two previously mentioned observations were confirmed: (1) The inner layers of the ventricular wall presented pure QS waves and (2) the total negative depolarization potential exceeded the total positive potential. An attempt was therefore made to interpret the significance of these observations.

Unipolar Leads. The absence of Q waves over subendocardial infarcts indicates that subendocardial depolarization is "silent" with respect to unipolar surface and precordial tracings. The absence of R waves in leads from the inner ventricular layers must indicate that subendocardial depolarization also is "silent" with respect to unipolar intramural tracings. Theoretically, a positive deflection should occur as the activation wave travels from the endocardium toward the intramural electrode, while a negative deflection would occur as the activation wave passes the electrode and proceeds toward the epicardium. Thus the downstroke of the negative deflection would appear as the muscle at the electrode is activated. In leads from the inner ventricular layers, however, activation of the region between the endocardium and the electrodes could not be recorded; that is, an initial R wave was not inscribed. Instead, the negative deflections began instantaneously. Activation of the inner layers therefore appears to occur instantaneously.

The significance of the pure QS waves in unipolar subendocardial leads may be restated

simply in relation to the theory of ventricular depolarization reviewed earlier. According to the theory, only the ventricular cavity and thin lining of endothelial cells should yield pure QS waves as they lie behind the activation front, on the negative side of the dipole, throughout depolarization. Actually, the inner layers of intramural muscle as well as the cavity and endothelium presented pure QS waves. Hence these layers also appear to lie behind the activation front throughout depolarization. Apparently, then, a recordable intramural activation front does not form until the inner ventricular layers have depolarized. Although this may not be true literally, it is true within the limits of the recording technics and equipment used in the present study. It should be noted that these experimental methods are more direct and more sensitive than those employed in routine clinical electrocardiography. If depolarization of the inner layers is not recorded in intramural lead oscillograms, it presumably would not be recorded in tracings from relatively remote sites registered on less sensitive apparatus. Subendocardial depolarization thus should not affect the clinical electrocardiogram.

In summary, depolarization of approximately the inner third of the ventricular wall fails to yield an R wave in unipolar intramural leads. Hence these layers presumably could not contribute to the R wave in unipolar surface and precordial leads. Contrary to classic theory, therefore, the R wave recorded over normal hearts must result entirely from depolarization of the outer two-thirds of the wall. Moreover, the middle third of the wall presents only a small r wave in intramural leads. Depolarization of the mid-ventricular muscle thus must be responsible for only a small proportion of the R wave over normal hearts. The observation that subendocardial infarcts do not alter the depolarization complex can thereby be explained. Since the normal complex results mainly from activation of the outer third of the wall, subendocardial lesions involving a large proportion of the ventricle would have little or no effect on the electrocardiogram.

Bipolar Leads. Bipolar leads were used in the following manner to demonstrate further the relative influence of various levels of the ventricle on the QRS complex in surface leads.

Electrodes were placed on the epicardial surface, in the cavity and at several intramural levels of the wall. Since different parts of the cavity yield tracings of different configuration, care was taken to locate the cavity electrode near the endocardium directly beneath the subendocardial electrode. After a complete set of unipolar records had been made, bipolar leads between the surface and cavity as well as between the surface and various intramural levels were recorded. In all instances the surface electrode was connected to the positive pole and the intramural or cavity electrode to the negative pole of the circuit. All tracings were registered on a Sanborn Twin-Beam electrocardiograph at a paper speed of 75 mm. per second.

The bipolar complexes obtained in these experiments represent potential differences between the ventricular surface and various lead-points in the underlying cavity and wall. Since the cavity does not participate in ventricular depolarization, it cannot actively contribute to the normal surface potential. Thus the contribution to surface potential made by different layers of the wall can be measured by comparing the various surface-intramural bipolar complexes with the surface-cavity bipolar complex. If activation of muscle between the cavity and the intramural lead-point affects the surface potential, the surface-intramural complex should be smaller than the surface-cavity complex. If muscle subjacent to the intramural lead-point does not affect the surface potential, the surface-intramural and surface-cavity complexes should be identical.

Unipolar tracings from the ventricular cavity, from intramural levels and from the surface were similar to those described previously. (Fig. 8.) The configuration of the bipolar tracings could be predicted from the unipolar leads. As shown in Figure 9, surface-subendocardial leads presented large R or Rs waves essentially identical with those in the surface-cavity lead. Thus the subendocardial muscle, like the cavity, does not actively contribute to the surface potential. Leads between the surface and mid-ventricular muscle, on the other hand, showed a slight decrease in size of the R wave as the intramural electrode was moved toward the surface. Hence these layers must play a minor role in determining the surface potential. Finally, when the intramural electrode reached the outermost ventricular layers, a marked change occurred in the size and shape of the bipolar complex. Activation of the outermost layers of the wall thus appeared primarily

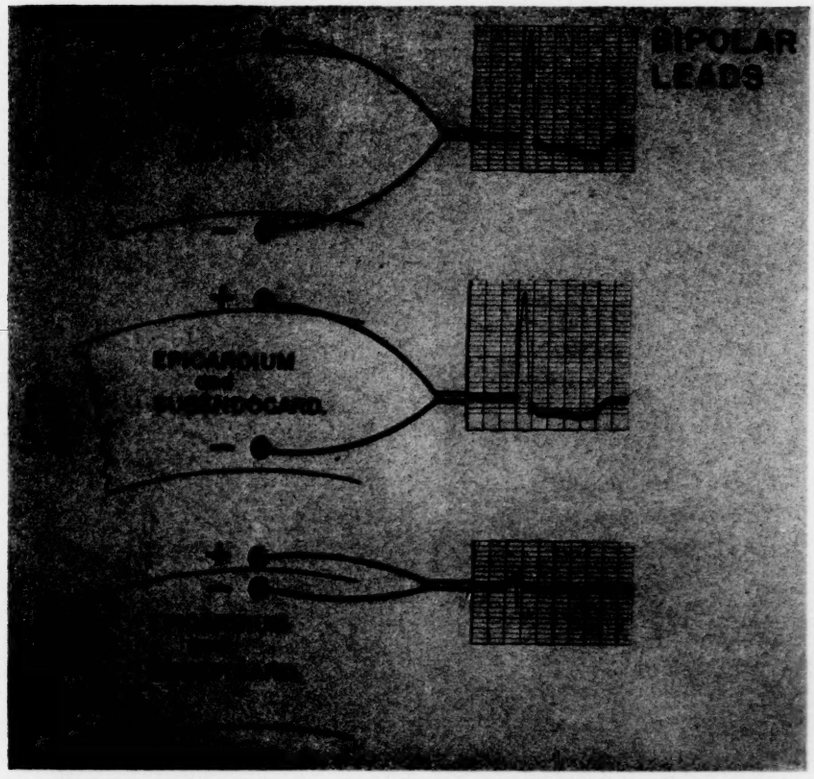


FIG. 9. Bipolar leads between A, epicardium and cavity; B, epicardium and subendocardial region; C, epicardium and subepicardial region. Same experiment as Figure 8. Epicardial-cavity complex consists of Rs wave identical with epicardial-subendocardial complex. These deflections should differ if depolarization of the subendocardial region affected the unipolar surface electrocardiogram. Epicardial-subepicardial complex is radically different from epicardial-cavity complex, suggesting that activation of the outermost ventricular layers is primarily responsible for the unipolar surface R wave.

responsible for the surface potential recorded over normal hearts.

Oscillographic Measurements of Approximate Rates of Depolarization. In order to determine why subendocardial depolarization is "electrocardiographically silent," an attempt was made to measure the relative speeds of depolarization at different intramural levels. Accurate measurement of depolarization rates was considered impracticable for several reasons. If lateral transmission occurs, as suggested by Durrer,[4] the rate of depolarization could not be determined unless the precise course of the activation wave were known. Moreover, explicit agreement has not been reached concerning the part of the downstroke in unipolar leads which corresponds to the passage of the activation wave beneath the electrode. Errors relating to this factor were minimized by timing three sites on the downstrokes: the onset, the termination, and either the mid-point or the point at which the deflection crosses the isoelectric line.

Intramural lead oscillograms were recorded at 1 to 2 mm. intervals from endocardium to epicardium of thirty transmural regions in eighteen animals. In each instance, analysis of the tracings showed that two more or less distinct zones could be defined: An inner zone which presented QS waves; and an outer zone which yielded definite R waves. (Fig. 10.) Depolarization of the inner zone of negativity was found to occur at speeds approximating several thousand millimeters per second. The rate of depolarization between successive layers of this zone often was immeasurable because the downstrokes of the QS waves occurred simultaneously. In contrast, the outer zone from which R waves were recorded depolarized at rates of 300 to 500 mm. per second. (Fig. 11.) These approximate figures were obtained whether the onset,

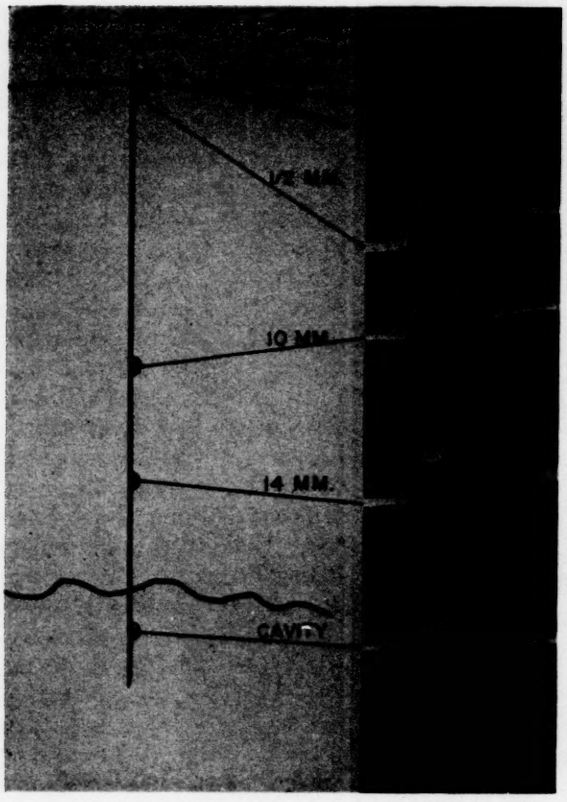


FIG. 10. Epicardial, intramural and cavity lead oscillograms from normal left ventricle. Thickness of wall measured 18 mm. from endocardium to epicardium. Intramural lead from subendocardial muscle presents a pure QS wave similar to cavity complex. Small r wave appears before the S wave at mid-ventricular level. Complex recorded immediately beneath epicardium exhibits RS wave resembling epicardial complex. Tracings recorded on DuMont cathode-ray oscillograph, type 322A, and photographed with Fairchild Oscillo-Record camera at speed of 150 mm. per second; 1 cm. equals 10 mv.

the termination, the isoelectric point or the mid-point of the downstroke was timed. Although the relative thickness of the two zones varied in different animals, the decrease in rate usually occurred in the middle third of the ventricular wall. Small r waves began to appear before the intrinsic deflection within 4 to 10 mm. from the endocardium of a typical region 16 mm. in thickness. Thus the inner ventricular layers were found to depolarize many times faster than the outer layers. This series of experiments will be reported in detail elsewhere.[18]

The foregoing observation may explain why subendocardial depolarization is "electrocardiographically silent." If the methods used to time the activation wave are valid, the subendocardial muscle appears to depolarize too rapidly to affect the electrocardiogram significantly. Activation of the endocardium via Purkinje fibers also is known to occur too rapidly to be recorded with standard electrocardiographic equipment. The rapid rate of subendocardial depolarization may indeed be attributable to extension of the Purkinje system a variable distance into the ventricular myocardium. This hypothesis is suggested by certain anatomic studies in experimental animals.[19]

Intramural leads from normal dog hearts have been recorded by Scher and associates,[20] Durrer[4] and Sodi-Pallares[21] as well as by the authors. Scher employed a compound tungsten electrode 0.3 mm. in diameter which could record from as many as fifteen levels between the cavity and epicardium. Unipolar and bipolar leads from the electrode were registered on a 16-channel cathode-ray oscillograph. The remarkable technical feat of recording from fifteen sites simultaneously makes it possible to compare potentials throughout the wall as they occur in a single beat. Compound tungsten plunge electrodes kindly supplied by Dr. Scher or made according to his instructions were among the several types used in the present investigation. Durrer recorded multiple unipolar and bipolar intramural lead oscillograms by means of a compound plunge electrode consisting of several silver wires within a hypodermic needle. His excellent study included exploration of the auricles as well as the ventricles. Both Durrer and Sodi-Pallares found that the inner ventricular layers depolarize more rapidly than the outer layers. The rates calculated by these workers are comparable to those reported from this laboratory.

COMMENTS

The seven pure subendocardial infarcts included in the present study might readily have escaped diagnosis. Contrary to classic theory, limb and precordial leads consistently failed to present abnormal Q waves. When the chest was opened, the entire ventricular surface from base to apex appeared normal. Direct leads from multiple sites on the ventricle, like the precordial tracings, contained R or Rs waves generally similar to those recorded from normal hearts. The absence of both visible lesions and electrocardiographic changes was, quite understandably, assumed to indicate that no infarction had occurred. It was thought that the surgeon had failed to tie the coronary artery

or that the tie had slipped so that coronary blood flow to the myocardium was not impaired. If the hearts had been abandoned upon completion of the electrocardiographic exploration, this erroneous conclusion would have remained uncorrected. The diagnosis of pure subendocardial infarction could be made only postmortem when the heart was sectioned.

Pure subendocardial lesions in human subjects likewise may cause no detectable electrical changes of depolarization hence their presence would not be suspected during life.[22] Since the infarcts underlie normal-appearing epicardium, they are easily overlooked even upon postmortem examination. The actual incidence of pure subendocardial infarction doubtless is greater than indicated by available clinicopathologic data. In our own experience in recent months we have observed two pure subendocardial lesions which could be diagnosed only after death. In both instances necropsy revealed involvement of the anterior wall of the left ventricle. Both patients, one of whom died of carcinoma of the stomach and the other of pneumonia, presented essentially normal QRS complexes in their electrocardiograms. More accurate statistics on the frequency of pure subendocardial infarcts can be obtained only if pathologic studies are made in large series of unselected hearts.

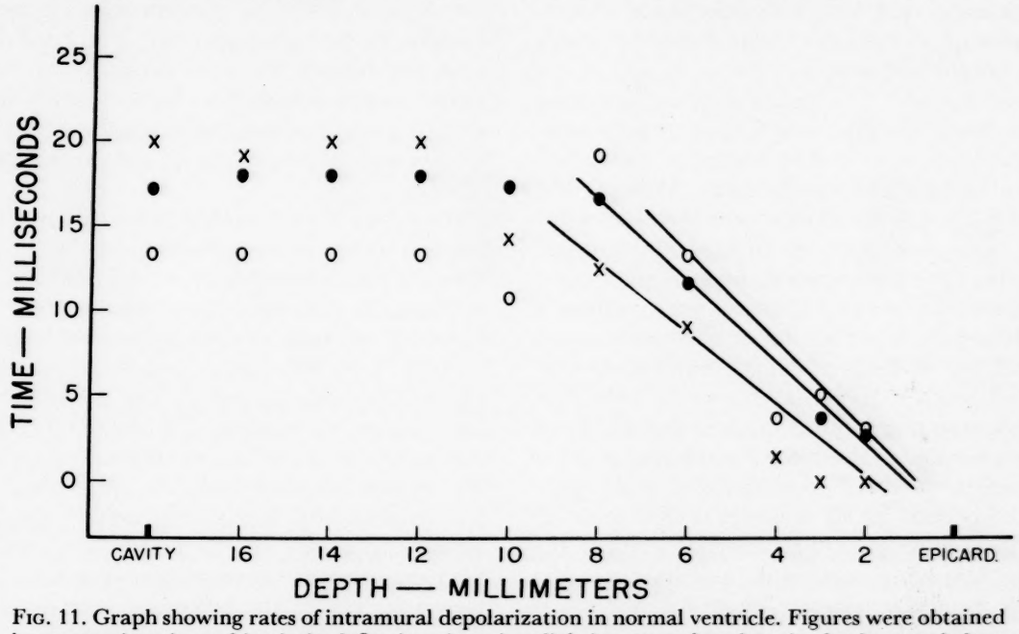


FIG. 11. Graph showing rates of intramural depolarization in normal ventricle. Figures were obtained by comparing time of intrinsic deflections in epicardial, intramural and cavity leads recorded on cathode-ray oscillograph. Three sites on the downstroke of each complex were timed: the onset, the termination and either the isoelectric point or the mid-point. X represents difference in time of onset of downstrokes in leads from successive layers of wall; ● represents difference in time of termination of downstrokes; ○ represents difference in time at which downstrokes cross isoelectric line in leads showing RS waves or reach their mid-point in leads showing QS waves. Thickness of wall approximated 18 mm. from endocardium to epicardium. Downstrokes recorded from inner 6 to 8 mm. of wall appeared to occur simultaneously whether onset, termination or mid-point was timed. This observation indicates that rate of depolarization in inner layers was too rapid to be measured. Rate of depolarization in outer 8 mm. of wall was between 360 and 450 mm. per second.

According to classic electrocardiographic theory, subendocardial infarcts should yield QR or notched QS waves in direct and precordial leads.[2d] During the present study, however, neither acute nor chronic subendocardial lesions presented abnormal Q deflections. The various factors which may account for this discrepancy between theory and fact are as follows:

Acute Lesions. Our failure to obtain abnormal Q waves over acute subendocardial lesions is consistent with the experimental findings of previous investigators.[5–9] Nevertheless, these results cannot be regarded as valid evidence refuting classic theory. As is widely recognized, acute experiments do not constitute a suitable method for studying QRS changes. Currents of injury during early stages of a lesion may cause marked RS-T segment deviation which obscures

the QRS complex. Acute infarcts in man likewise may fail to present abnormal Q waves, either because of distortion by injury currents or because the metabolic alterations responsible for QRS changes had not yet occurred when the electrocardiograms were made. Thus the QRS complex associated with subendocardial infarction can be accurately determined only by observations on chronic lesions.

Chronic Infarcts. As noted earlier, previous workers have reported conflicting results concerning the depolarization complex associated with subendocardial infarction. Wilson obtained QR or notched QS waves over subendocardial extensions of a chronic transmural infarct in the dog. Several investigators likewise recorded abnormal Q waves over regions of chronic subendocardial infarction in human hearts. These findings are consistent with classic theory. In other patients, however, subendocardial lesions were found to yield normal R or Rs waves similar to those obtained in the present experiments. Several explanations were proposed to account for the absence of abnormal Q waves over clinical subendocardial lesions: (1) Infarcts involving opposing portions of the ventricle produce opposite electrical affects on the precordium. Thus Q waves may fail to occur over subendocardial lesions if more than one aspect of the wall is involved.[10] (2) Normal R or Rs deflections may be registered over ring-like subendocardial infarcts extending around the entire circumference of the cavity. Under such circumstances the negative cavity potential presumably does not begin until the subepicardial region is activated. Cavity negativity cannot, therefore, be transmitted to the surface.[14] (3) If left bundle branch block is present, the left cavity is initially positive, thereby preventing the occurrence of Q waves over anterolateral infarcts.[12b] (4) Displacement of the transitional zone because of rotation of the heart may obscure characteristic QRS changes in precordial leads.[12a] (5) If a subendocardial lesion is extremely small, it may fail to affect the distant precordial electrode.[10]

Of the preceding factors, none explains the absence of Q waves over chronic subendocardial infarcts in our experiments. All seven lesions were old enough to allow the evolution of permanent electrocardiographic and histologic changes. The RS-T segments in direct and precordial leads were essentially isoelectric, indicating that injury currents had ceased. In no instance were opposing aspects of the ventricle or the entire subendocardial rim involved. Left bundle branch block was not present. Rotation of the heart could not account for the absence of Q waves in the many epicardial and precordial leads taken. Several of the lesions were of considerable magnitude. Finally, surface tracings were registered directly over the infarct in every instance. Since these leads record essentially local potentials, they should present abnormal complexes even if the lesions are too small to affect precordial electrodes.

The fact remains that pure subendocardial infarcts in the present series consistently yielded normal electrocardiograms. Wilson and other workers, in contrast, have reported the occurrence of abnormal Q waves over regions of chronic subendocardial infarction. Moreover, several animals studied in this laboratory have been found to present QR or QS waves over subendocardial extensions of transmural lesions. These observations indicate that coronary Q waves occur only when dead muscle is present in superficial layers of the heart. With few possible exceptions the cases of subendocardial infarction described in the literature were not "pure." Those lesions from which pathologic Q waves were recorded apparently reached the ventricular surface.

The absence of Q waves over pure subendocardial infarcts is explained by the diagrams in Figure 12. As discussed in Part II of the present paper, the inner layers of the normal ventricular wall appear to be "electrocardiographically silent." (Fig. 12B.) The normal electrocardiogram results from activation of the outer layers of the heart. (Fig. 12C-F.) Lesions confined to the "silent" zone, such as the pure subendocardial infarcts in our experiments, thus have no effect on the QRS complex. Subendocardial infarction in hearts with some epicardial involvement, on the other hand, may be associated with QRS alterations. In these instances the abnormal Q waves are not related to the subendocardial infarction. They represent changes in the outer ventricular layers which determine the electrocardiogram.

If depolarization of the outer ventricular layers causes the R wave in epicardial leads, as represented in Figure 12, this deflection should disappear or become markedly smaller when the outer layers are inactivated. Such changes in the epicardial complex have been reported by Bellet

and Johnston[23] following the production of epicardial burns. Similar results were obtained in this laboratory by excision or traumatization of the outer layers.[24] Variable amounts of subepicardial muscle were cut away or burned, damaged area exhibited pure QS waves, QR waves or abnormally small r waves in some instances. Despite these marked changes in the epicardial complex, the inner ventricular layers were entirely normal. Thus the QRS complex

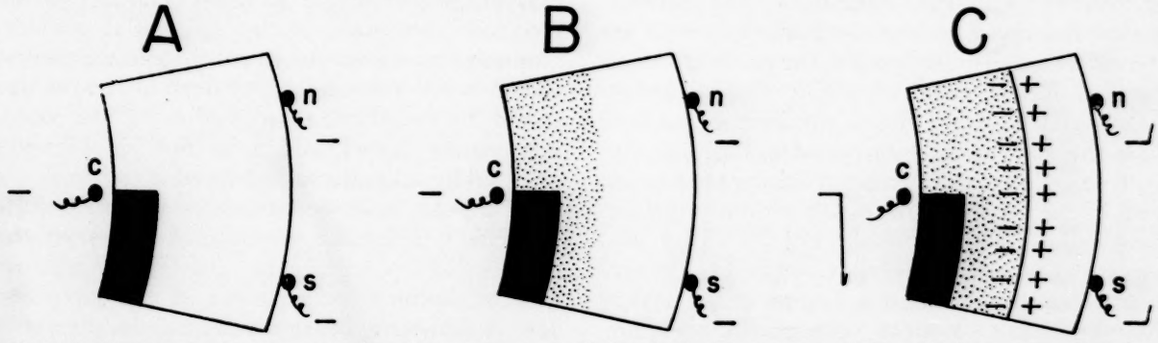


FIG. 12. Diagrammatic representation of various stages of depolarization in a ventricle exhibiting pure subendocardial infarct. Black area corresponds to infarct. Clear area is resting (polarized) muscle, stippled area is depolarized muscle. Ventricular cavity to left of each diagram, epicardial surface to right. Direction of depolarization is from endocardium to epicardium. The activation front is represented according to convention as a series of dipoles, the positive poles (+) preceding and the negative poles (−) immediately behind the front. Electrode *c* is in cavity. Electrode *s* is on epicardial surface over subendocardial infarct. Electrode *n* is on surface over normal muscle. A, entire ventricular wall, with the exception of the infarcted region, is completely polarized. Since no electrical activity is present in the ventricle, the cavity and surface leads remain isoelectric. B, onset of depolarization. Contrary to classic theory, depolarization of the ventricular wall does not proceed at a constant rate from endocardium to epicardium. Rather, the inner layers appear to depolarize instantaneously or almost simultaneously. Therefore, these layers are "electrocardiographically silent," as their activation is too rapid to affect the surface and cavity electrodes. In contrast, the remainder of the myocardium will depolarize at measurable rates in an essentially unidirectional manner. C, early in the period of depolarization. The activation front is shown at boundary between depolarized and resting muscle. Abrupt downstroke occurs in cavity lead as it faces negative side of activation front. In accordance with electrophysiologic laws, the cavity will become progressively less negative as the front travels away from it. The epicardial surface is weakly positive since it faces but is relatively distant from the positive side of the activation front; it will become progressively more positive during the rest of depolarization. Since the subendocardial infarct is located entirely within the electrocardiographically silent zone, surface electrodes *n* and *s* register identical potentials.

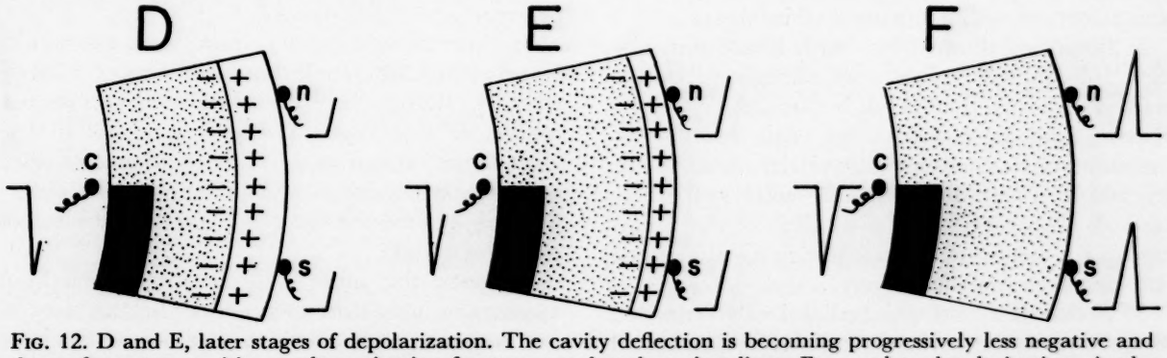


FIG. 12. D and E, later stages of depolarization. The cavity deflection is becoming progressively less negative and the surface more positive as the activation front approaches the epicardium. F, complete depolarization. As the depolarization process reaches the epicardial surface directly beneath electrodes *n* and *s*, an intrinsic deflection occurs in the surface leads and the tracings become isoelectric. The complexes in leads *n* and *s* are identical, consisting of normal R waves.

after which the chest was closed for a period of one to three weeks. In other animals acute subepicardial damage was inflicted with formaldehyde or nitric acid. Following these procedures, epicardial leads over the excised or appeared to depend upon the status of the outer layers of the ventricle.

The preceding discussion throws emphasis on certain well known limitations of clinical electrocardiography. As observed by every

cardiologist, many patients with serious heart disease present essentially normal electrocardiograms. Other individuals with good myocardial function show "coronary" Q waves in multiple leads. Such puzzling findings may be explained by differences in the influence of the various myocardial layers on the electrocardiogram. As demonstrated experimentally, the outer layers of the wall appear to be primarily responsible for the normal R wave. Hence the location rather than the size of a lesion must determine the electrocardiographic picture. Widespread lesions deep in the myocardium which seriously impair myocardial function would fail to cause abnormal Q waves. Conversely, relatively benign lesions involving the outer ventricular layers may produce radical electrocardiographic changes. These considerations clearly show the danger of reliance upon the electrocardiogram as the sole means of diagnosing myocardial disease. As observed by Wilson, clinical electrocardiography must be regarded merely as a diagnostic technic of limited value in supplementing the information gained from a careful study of the patient's history, physical findings and clinical course.

SUMMARY AND CONCLUSIONS

1. The literature concerning subendocardial infarction occurring in man and experimentally produced in animals is reviewed. Previous workers obtained a variety of QRS patterns over subendocardial portions of infarcts.

2. Electrocardiographic and histologic observations in seven dogs with chronic subendocardial infarcts produced by coronary artery ligation and in twelve dogs with acute subendocardial lesions produced by burns are described. These infarcts were solely subendocardial, including up to two-thirds of the thickness of the wall but in no instance involving the outermost ventricular layers.

3. Precordial and epicardial leads recorded directly over the seven chronic subendocardial infarcts consistently exhibited normal R or Rs waves. The twelve examples of acute subendocardial necrosis likewise always failed to yield abnormal Q waves. These observations indicate that subendocardial muscle does not affect the depolarization complex in epicardial or precordial leads.

4. The electrocardiographic effects of subendocardial muscle in the normal dog heart are considered. Unipolar intramural lead electrocardiograms and oscillograms recorded throughout the inner ventricular layers presented pure QS waves. Tracings from the outer ventricular layers showed RS waves. An increase in width and amplitude of the R wave occurred as the electrode approached the epicardial surface. Contrary to classic electrocardiographic theory, the R wave recorded over normal hearts was found to result from activation of the outer ventricular layers and was not significantly affected by subendocardial depolarization.

5. Bipolar leads were recorded to demonstrate the effect of various intramural layers on the surface electrocardiogram. The bipolar tracings indicated that depolarization of the outermost few millimeters of the ventricle is primarily responsible for the normal surface R wave.

6. Approximate rates of intramural depolarization were measured by means of cathode-ray oscillograms. Depolarization of the inner ventricular layers was found to occur at rates approximating several thousand millimeters per second. The outer ventricular layers depolarized at rates of about 300 to 500 mm. per second. Subendocardial depolarization may fail to affect the electrocardiogram because it occurs too rapidly to be recorded.

7. The absence of abnormal Q waves over subendocardial infarcts in the present series is attributed to the fact that the outer ventricular layers remained entirely intact. The normal R wave resulting from depolarization of these layers was therefore recorded.

8. Pure subendocardial infarcts do not significantly alter the depolarization complex. Consequently, it may be impossible to diagnose old lesions of this type in man by means of the electrocardiogram alone. The incidence of pure subendocardial infarction probably is considerably higher than indicated by reported clinicopathologic data.

9. Since the inner ventricular myocardium appears to have little or no effect on the electrocardiogram, clinical electrocardiography is of limited value in the diagnosis of myocardial disease which does not involve superficial layers of the heart.

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Studies on the Mechanism of Ventricular Activity*

VII. The Origin of the Coronary QR Wave

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An important diagnostic sign of coronary artery occlusion is the appearance of QR waves. These abnormal complexes frequently occur in chest leads from patients with anterior infarcts. According to classic electrocardiographic theory the coronary QR wave is associated with subendocardial infarction.[1] The initial Q wave is believed to result from transmission of negative cavity potentials through dead subendocardial muscle. Activation of the overlying myocardium causes the final R wave.

Results conflicting with this theory were obtained in the experimental study of myocardial infarction described in the preceding paper.[2] By means of coronary artery ligation, pure subendocardial infarcts involving up to two-thirds of the thickness of the ventricular wall were produced in seven dogs. These seven chronic infarcts consistently failed to yield abnormal QR waves. Instead, normal R or Rs waves were found in all leads from the ventricular surface and precordium directly over the infarcts. Acute subendocardial burns in twelve animals likewise yielded no abnormal Q deflections. Since the subendocardial lesions did not cause QR waves, a modification of classic theory concerning the genesis of these complexes appeared necessary. The present study was therefore designed to determine under what circumstances coronary QR waves do occur.

MATERIALS AND METHODS

A total of sixty-eight chronic infarcts were produced in large dogs by ligation of the anterior descending coronary artery. The electrocardiographic equipment and recording methods used to study these lesions have been described in a previous report.[3a] Several days to weeks after ligation routine precordial leads were made. The chest was then opened and multiple direct epicardial leads were registered simultaneously with a cavity lead from each infarcted ventricle. In most experiments intramural and cavity tracings were recorded directly subjacent to the surface lead-points. A tiny plunge electrode was used to obtain the intramural and cavity records.

An attempt to elicit injury currents was made in each instance by pressing the ventricular surface with a sharp instrument. This technic, employed by Wilson,[4] provides a reliable means of differentiating live and dead muscle. If electrically active tissue is present at or near the surface electrode, marked elevation of the RS-T segment occurs upon pressure. If the muscle is completely dead, the RS-T segment remains isoelectric. Similarly, viable muscle at intramural lead-points causes RS-T segment elevation in the intramural tracings. No elevation occurs if the intramural muscle is dead. The intramural injury current is elicited by the sharp tip of the plunge electrode. RS-T segment elevation gradually declines following insertion of the plunge electrode, usually reaching a minimum or disappearing within two to ten minutes. By means of injury currents it was thus possible to demonstrate viable cardiac muscle not only at the ventricular surface but also at any intramural level.

Histologic Methods. Upon completion of the electrocardiographic exploration specimens from

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the infarcted ventricle were cut and fixed in formaldehyde for several days. Histologic sections of selected regions were then made in duplicate. Each section was stained with hematoxylin and eosin as well as with a connective tissue stain. When viewed under the microscope the stained sections exhibited a variety of patterns. Four histologic grades were defined: Grade I, normal-appearing myocardium with clearly defined striae, cross-striae, nuclei and nucleoli; Grade II, relatively minor damage manifested by a moderate number of pyknotic nuclei, some loss of striae and cloudy swelling; Grade III, more pronounced damage consisting of absence or pyknosis of most nuclei, some vacuolization, marked loss of striae and/or cellular infiltration; Grade IV, complete fibrosis or necrosis. Hemorrhage or pericarditis was described when present. In no instance did the observer know the electrocardiographic appearance of the section being graded. If difficulty was encountered in grading a section, the slides were reviewed by several observers before a histologic classification was made.

An attempt to evaluate the significance of histologic changes was made by means of control experiments in normal hearts. In five animals the entire surgical procedure attendant to coronary artery ligation was carried out but the artery was not tied. Two to three weeks later the heart was removed and histologically examined. In four other normal animals the chest was opened under anesthesia, immediately after which the heart was removed for routine histologic study. Sections from four of the nine control hearts showed Grade II changes consisting of pyknotic nuclei, loss of striae and cloudy swelling. Somewhat more marked alterations were seen in a few areas. Thus it was impossible to determine whether such changes in infarcted ventricles resulted from coronary artery occlusion, from exposure, manipulation or other trauma incident to the experiment or possibly from a pre-existing myocarditis.

No attempt was made to reconstruct entire infarcts by histologic methods. The direct leads recorded during the experiments represented essentially local potentials.[3] Hence a single transmural section containing the lead-point was considered adequate for purposes of correlating electrocardiographic and histologic data. As sections are two-dimensional, the specimens examined may have differed histologically from myocardial tissue in adjacent planes of the ventricular wall. This possibility was minimized by comparing the histologic description of each section with gross descriptions of the surrounding myocardium.

RESULTS

Of the sixty-eight infarcts in the series only twenty-three were selected for the present study of coronary QR waves. At least one surface lead from each of these lesions contained deep, wide Q deflections followed by a distinct R component. Well stained histologic slides of the myocardium underlying the lead-point were available in all instances. In order to avoid ambiguity, complexes of the following types were not classified as coronary QR waves: (1) QS waves with slurs or with embryonic r waves which failed to reach the baseline; (2) qR waves which may have been within normal limits. Although such deflections were not obtained in direct surface leads from normal hearts studied in this laboratory, a small q wave theoretically may precede the normal surface R wave; (3) complexes exhibiting slight initial positivity which could be construed as an r wave.

In three of the twenty-three infarcts (Table 1, experiments 8, 33 and 53), definite QR waves were registered in two surface leads. Only one lead from each of the remaining twenty-one lesions was considered suitable for analysis. Thus the following data concern a total of twenty-six surface leads containing coronary QR waves.

Correlation of QR Waves with Gross Pathology. The twenty-six sites which yielded surface QR waves were termed "coronary QR lead-points." *Gross inspection of the ventricular surface revealed that all twenty-six QR lead-points were located near or directly over dead muscle.* In twenty-one of the twenty-three ventricles QR waves were recorded at or near the edges of transmural infarcts while QS waves appeared over the center. Figure 1 shows a typical instance in which the edge of the lesion yielded QR waves. Four transmural infarcts exhibited QR waves over the center as well as over the edges. These infarcts were of the patchy type presenting a speckled appearance characteristic of mixtures of live and dead tissue.

Transmural regions of the myocardium directly beneath QR lead-points were termed "coronary QR regions." Eleven of the twenty-six QR regions exhibited subendocardial infarction. (Fig. 2.) Nine regions appeared grossly

normal at all levels from endocardium to epicardium. (Fig. 3.) Six regions presented variable amounts of viable muscle interspersed with dead tissue. (Figs. 1 and 4.) Subendocardial levels of the QR regions thus appeared completely dead in some instances, completely normal in other instances and partially dead in the remaining instances. This wide variation was clearly seen in one section which contained two QR regions. (Fig. 5.) The subendocardia muscle appeared entirely dead in one region (lead A) and entirely normal in the adjacent region (lead B). *From a comparison of the twenty-six QR regions, it was thus evident that coronary QR waves could not be correlated with the gross appearance of the deeper ventricular layers.*

TABLE I

PATHOLOGIC FINDINGS ASSOCIATED WITH SURFACE QR WAVES

(1) Experiment No.	(2) Days after Ligation	(3) Location of QR Region	(4) Histology of QR Region	
			(a) Superficial Layers	(b) Subendocardial Layers
7	11	Subendocardial extension of through-and-through infarct	Grade III	Two-thirds of wall Grade IV
8a	27	Edge of patchy infarct	Grades I & IV	Grades I & IV
8b	27	Subendocardial extension of patchy infarct	Grades II–III	Four-fifths of wall Grade IV
9	13	Subendocardial extension of through-and-through infarct	Grade I	One-fourth of wall Grade IV
10	19	Adjacent to through-and-through infarct	Grades I–II	Grades I–II
11	26	Subendocardial extension of through-and-through infarct	Grade III	Four-fifths of wall Grade IV
12	29	Adjacent to patchy infarct	Grade II	Grade I
14	33	Adjacent to through-and-through infarct	Grades II-III	Grades II-III
17	58	Edge of patchy infarct	Grade II with strands of IV	Grade I
22	78	Adjacent to through-and-through infarct	Grades II–III	Grade I
24	80	Adjacent to through-and-through infarct	Grade III	Grades I–II
26	23	Subendocardial extension of through-and-through infarct	Grade I	One-third of wall Grade IV
33a	11	Subendocardial extension of through-and-through infarct	Grade II	Two-thirds of wall Grade IV
33b	11	Adjacent to through-and-through infarct	Grade II	Grades I–II
38	17	Subendocardial extension of patchy infarct	Grades I–II	One-fourth of wall Grade IV
39	19	Edge of patchy infarct	Grades III–IV	Grades I & IV
40	20	Center of patchy infarct	Grades III–IV	Grades II & IV
46	29	Adjacent to through-and-through infarct	Grades I–II	Grades I–II
50	24	Adjacent to patchy infarct	Grades II-III	Grade III
51	49	Subendocardial extension of through-and-through infarct	Grade II with strands of IV	One-fourth of wall Grade IV
52	54	Subendocardial extension of through-and-through infarct	Grades II–III with strands of IV	One-third of wall Grade IV
53a	35	Subendocardial extension of patchy infarct	Grade I with strands of IV	One-half of wall Grade IV
53b	35	Edge of patchy infarct	Grades II & IV	One-third of wall Grade IV
54	38	Edge of patchy infarct	Grades III & IV	Grades II & IV
55	28	Adjacent to patchy infarct	Grade II with few strands of IV	Grade I with few strands of IV
57	48	Subendocardial extension of through-and-through infarct	Grade III with strands of IV	Two-thirds of wall Grade IV

Correlation of QR Waves with Histopathology. Microscopic examination of the QR regions

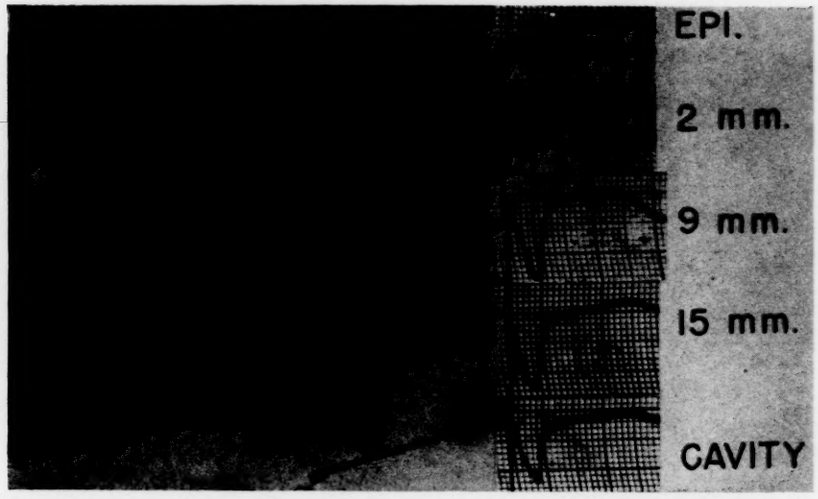


FIG. 1. Infarct twenty-seven days after coronary artery ligation. Magnification × 6. Tracings recorded at paper speed of 125 mm. per second. Attenuation × 20. Sensitivity: 20 mv. equal 15 mm. Black line indicates path of plunge electrode. Infarcted tissue appears whitish gray, viable muscle grayish black. Section shows gross appearance of QR region. Patchy transmural infarct to right of section, normal muscle to left. QR wave was recorded over the edge of the infarct. A variable mixture of live and dead muscle appears at surface and at all intramural levels of QR region.

yielded data generally consistent with the gross findings. Eleven regions exhibited subendocardial necrosis or fibrosis varying in extent from a narrow endocardial layer to almost the entire thickness of the wall. Nine of these eleven regions showed a variable degree of damage at superficial levels, consisting of Grade II and III changes and/or strands of fibrosis. In the remaining two instances (experiments 9 and 26) the superficial muscle appeared completely normal.

The eleven regions of subendocardial infarction showed no relationship between the size of the surface Q wave and the extent of the infarct. Deep, wide Q waves were recorded over several regions which contained only a thin layer of dead subendocardial muscle. On the other hand, small Q waves occurred over some regions of subendocardial infarction involving more than half the thickness of the wall. (Fig. 2.) This observation is inconsistent with the classic theory of the genesis of coronary QR complexes. If the Q component resulted from transmission of negative cavity potentials through dead subendocardial muscle, it should vary in size with the thickness of the subendocardial infarct.

Nine QR regions showed little or no histologic evidence of infarction. Pyknotic nuclei, loss of striae (Grades II and III) and/or strands of

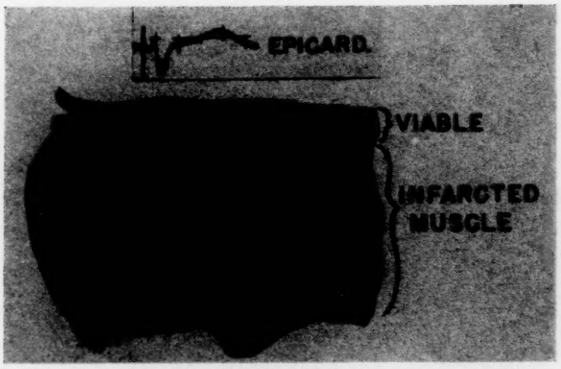


FIG. 2. Subendocardial extension of transmural infarct. Only a thin layer of superficial muscle remains viable. Although almost the entire thickness of the wall is infarcted, the surface Q wave is extremely small.

fibrotic tissue were seen at various levels. These changes were minimal in some instances, more marked in others. Completely normal muscle was found throughout the subendocardial layers of several regions. Figures 6 and 7 show the histologic appearance of grossly normal subepicardial and subendocardial muscle in a QR region. Grade II and III changes appear at subepicardial levels (Fig. 6) while the subendocardial layers are histologically normal. (Fig. 7.)

Six QR regions presented a patchy mixture of viable and necrotic or fibrotic tissue. The amount and distribution of dead muscle varied

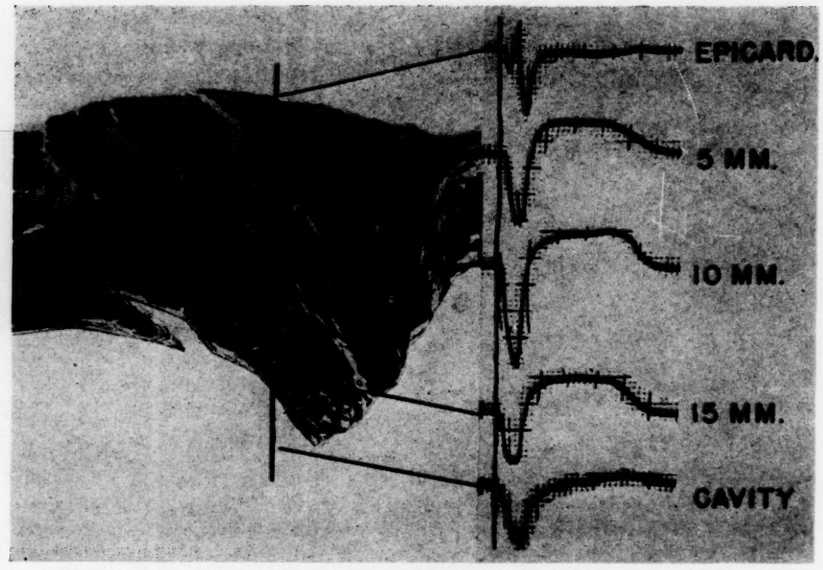


FIG. 3. Section from ventricle seventy-eight days after coronary artery ligation. QR region appears grossly normal at all levels from endocardium to epicardium. Histologic examination showed mild to moderate changes at subepicardial level. Subendocardial muscle was histologically normal. A sharply demarcated through and through infarct (not shown in section) was present to left of QR region.

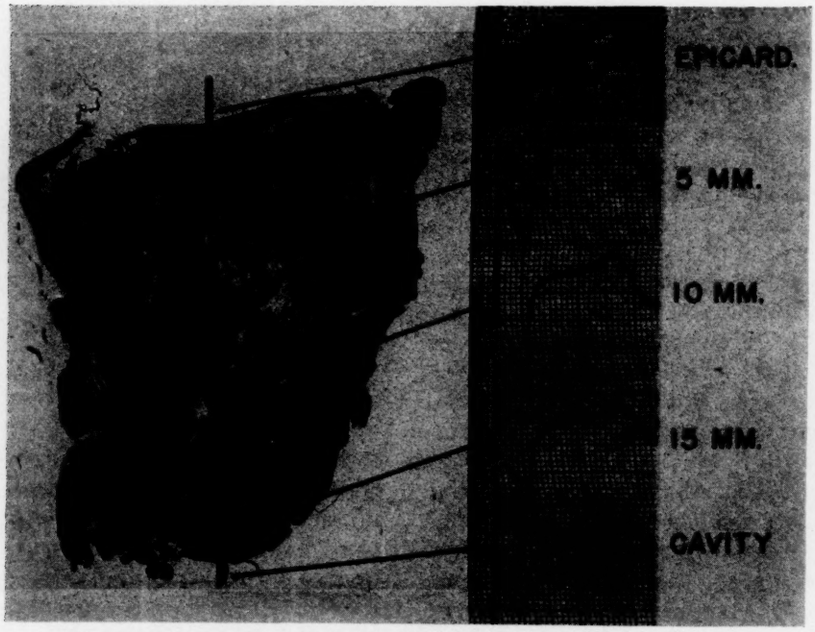


FIG. 4. Region of sandwich-like patchy infarction fifty-eight days after coronary artery ligation. A large fibrous extension of adjacent transmural infarct appears at mid-ventricular level. Approximately the middle third of the QR region is dead. Subendocardial muscle beneath fibrosis is normal. Subepicardial muscle in QR region is viable but moderately altered, showing Grade II histologic changes and scattered strands of fibrosis.

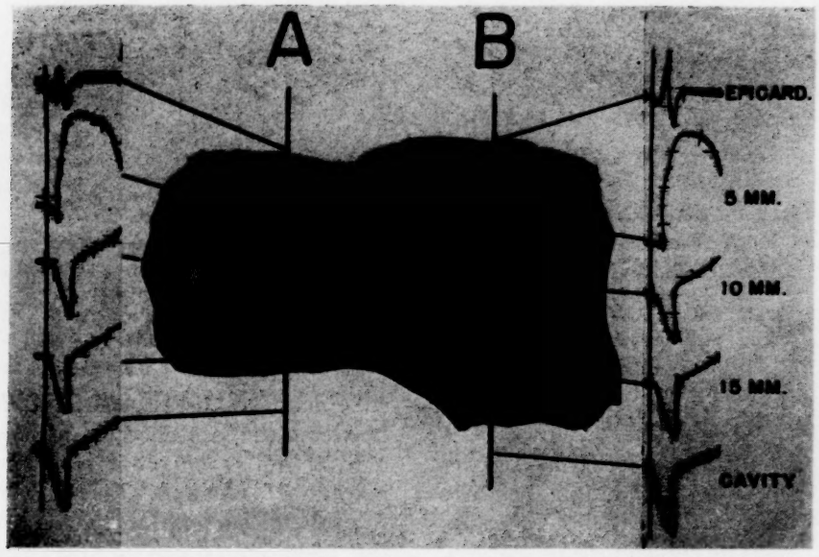


FIG. 5. Section from ventricle eleven days after coronary artery ligation. A large through and through infarct was present to left of lead-point (A). Section includes two QR regions. QR region to left (A) shows subendocardial infarction involving inner two-thirds of wall. QR region to right (B), in contrast, is grossly normal at all levels from endocardium to epicardium. Coronary QR waves thus occurred in this experiment over normal subendocardial muscle as well as over subendocardial portions of the infarct. Intramural tracings at 5 mm. depth were recorded immediately after insertion of plunge electrode. Marked RS-T elevation in these leads establishes the presence of viable muscle at superficial levels of QR regions.

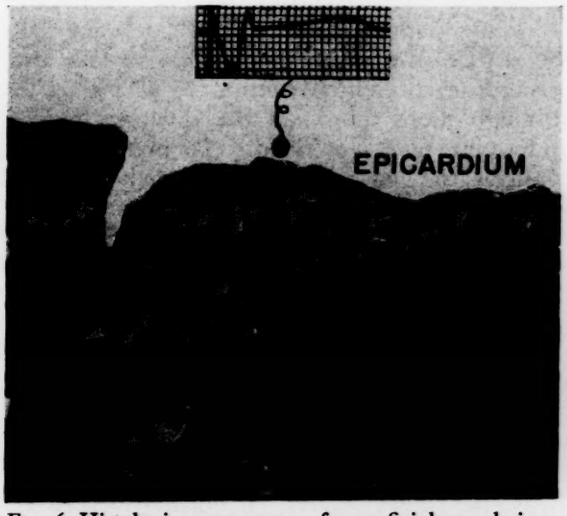


FIG. 6. Histologic appearance of superficial muscle in a QR region. Surface QR wave recorded over region shown at top. The muscle appeared normal upon gross inspection. Histologic examination revealed pyknosis and loss of nuclei, loss of striae, cloudy swelling, vacuolization and cellular infiltration (Grades II and III).

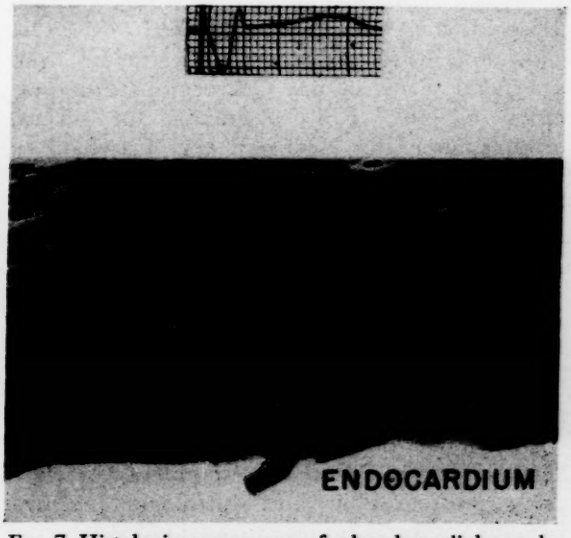


FIG. 7. Histologic appearance of subendocardial muscle from same region as Figure 6. Although surface QR wave was obtained over region, the subendocardial layers appear completely normal. Note differences in cellular structure, nuclei and striations between subendocardial muscle in this illustration and superficial muscle shown in Figure 6.

considerably. For example the QR region in experiment 8a (Fig. 1) consisted throughout of normal muscle interspersed with fibrous strands extending from an adjacent region of more severe infarction. Experiment 17 (Fig. 4), in contrast, yielded a QR region of sandwich-like infarction presenting a large area of fibrosis between

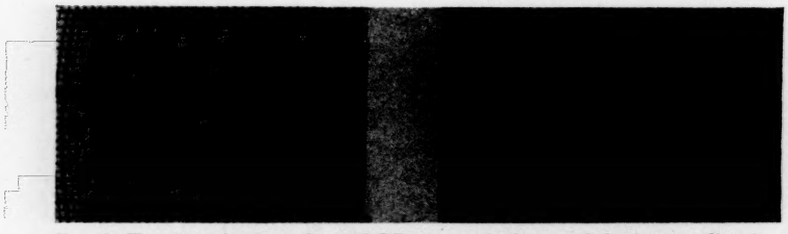


FIG. 8. Tracings from surface of QR region before and during application of pressure. QR wave followed by isoelectric RS-T segment was recorded with cotton-tipped electrode. When the surface was pressed, marked elevation of the RS-T segment occurred. RS-T elevation, indicating injury effects, established the presence of live muscle beneath the electrode.

moderately altered epicardium (Grade II) and normal subendocardial muscle.

Microscopic examination, like gross inspection, failed to reveal a correlation between coronary QR waves and the status of subendocardial tissue. As seen in column 4b of Table 1, the deeper levels of the QR regions varied from completely normal to completely dead. *The only histologic feature common to all twenty-six QR regions was the presence of some viable muscle at superficial levels. Some dead muscle also was always seen at superficial levels in or near the QR regions.*

Current of Injury. Marked RS-T segment elevation, indicating current of injury, always occurred when pressure was applied to the QR lead-points. (Fig. 8.) Intramural tracings from superficial levels of the QR regions also presented elevated RS-T segments for several minutes after the electrode was inserted. In Figure 5A and B the intramural tracings at 5 mm. depths were recorded before injury currents had diminished. The RS-T segments in these tracings are greatly elevated, establishing that live muscle was present at superficial levels of the wall. Thus the persistence of viable muscle in the outer layers of the QR regions was demonstrable by electrocardiographic as well as histologic methods.

Subendocardial levels of the QR regions likewise showed a close correspondence between electrocardiographic and histologic findings. In some instances injury currents failed to occur when the electrode was plunged into the deeper intramural layers. These instances were found to present subendocardial necrosis or fibrosis. In other QR regions subendocardial tracings presented RS-T segment elevation. The subendocardial layers of these regions showed variable amounts of uninfarcted muscle. As in normal hearts,[3] the viable subendocardial tissue yielded weaker injury currents than viable subepicardial tissue. No relationship existed between the presence or absence of subendocardial injury currents and the occurrence of coronary QR waves. This observation confirms the lack of correlation between QR waves and the histologic status of the deeper ventricular layers.

COMMENTS

Coronary QR waves commonly are believed to occur where the subendocardial layers of the ventricle are dead and the outer layers are uninfarcted. Contrary to this theory, the pure subendocardial infarcts described in Part 1 of the preceding paper failed to yield coronary QR waves.[2] Leads from the ventricular surface and precordium presented normal R or Rs waves although more than half the thickness of the underlying wall was dead. The present study confirms the lack of correlation between QR waves and subendocardial infarction. Of the twenty-six QR regions examined only eleven contained completely dead subendocardial muscle. The remaining fifteen QR waves appeared over regions in which the inner layers showed completely normal muscle or a mixture of live and dead tissue. These findings indicate that coronary QR waves are independent of the status of the deeper ventricular layers. Support for this conclusion has been obtained by cutting away the outer layers of normal ventricles. Although the entire subendocardial region remained intact, QR waves sometimes occurred over the edges of the cut.[5]

Since coronary QR waves could not be correlated with the status of subendocardial muscle, attention was directed to subepicardial levels of the twenty-six QR regions. Here two characteristics were present in every instance studied: (1) Significant amounts of dead muscle could be demonstrated at or near the sites from which

surface QR waves were obtained. (Table 1, column 3.) (2) As shown by injury currents (Figs. 5 and 8) and by histologic examination (Table 1, column 4a), the muscle beneath the electrode was never completely dead. *Both live and dead muscle in the outer ventricular layers thus appear essential to the production of coronary QR waves.*

Why should this particular pathologic situation give rise to coronary QR complexes? An answer is suggested by experimental observations on the role of subendocardial muscle in the normal electrocardiogram. Since subendocardial infarcts did not alter the depolarization complex in leads from the ventricular surface or precordium, subendocardial depolarization was considered to be "electrocardiographically silent." This conclusion was supported by the study of normal ventricles reviewed in Part II of the preceding paper.[2] Pure QS waves appeared in intramural leads from the subendocardial layers. Such deflections theoretically occur as the activation process travels away from the electrode. Activation of the subendocardial muscle thus had no apparent effect on the tracings. The rate of depolarization, as measured with cathode-ray oscillographs, appeared to be much more rapid in the inner ventricular layers than in the outer layers. Subendocardial depolarization may therefore be "electrocardiographically silent" because it is too rapid to be recorded.

Regardless of their explanation the preceding observations on infarcted and normal subendocardial muscle indicate that the inner ventricular layers do not contribute to the depolarization complex. Activation of the outer layers thus must be primarily responsible for the R wave recorded over normal hearts. It follows that an R wave would not occur if the outer layers were entirely inactivated. Conversely, unless these layers were at least partially inactivated, an abnormal complex (initial Q wave) could not occur. Hence a mixture of electrically active and electrically inactive muscle in the outer layers would be necessary to yield coronary QR waves. This simple hypothesis accounts for all the results obtained in the experimental studies of QR waves, of subendocardial infarcts and of normal hearts.

The methods used in the preceding experimental studies are more direct and more sensitive than those employed in clinical electrocardiography. Since subendocardial depolarization could not be recorded in the experiments, it would therefore not be expected to affect the clinical electrocardiogram. Under such circumstances electrocardiographic theory concerning the QR waves associated with clinical myocardial infarction would require modification. A theoretical explanation of precordial QR waves consistent with the experimental findings is illustrated diagrammatically in Figure 9. This explanation is later extended to account for the abnormally small r and rS waves as well as various types of QS waves often seen in patients with myocardial infarcts. It should be noted that the diagrams and explanations are necessarily oversimplified. Ventricular depolarization actually is a complicated, three-dimensional process which cannot be accurately represented in two-dimensional drawings of transmural muscle strips.

Precordial QR Waves. Theoretically, QR waves may occur in precordial leads when the angle subtended by the electrode includes both live and dead subepicardial muscle. This situation may exist when the ventricular wall beneath the electrode contains any of three common types of infarction: (1) A broad transmural lesion bordered by normal muscle (Fig. 9A); (2) a transmural infarct with subendocardial extensions. (Fig. 9B.) Since subendocardial portions of the lesion apparently do not affect the depolarization complex, these two types of infarction should yield identical depolarization waves; (3) a large patchy infarct. (Fig. 9C.) In all three instances a negative depolarization potential is transmitted from the cavity and subendocardial region through dead subepicardial muscle to the ventricular surface. At the same time a positive surface potential is contributed by live subepicardial muscle. The precordial complex represents a summation of the negative and positive surface potentials. It may therefore consist of a QR wave. Whether or not such complexes actually occur depends upon several factors:

1. Early in depolarization, the transmitted negative potential must be of greater magnitude than the positive potential. Otherwise an initial Q wave will not occur. Later in depolarization the positive potential must exceed the negative potential in order to produce an R wave. Thus a coronary QR wave is most likely to appear when the positive surface potential reaches its maximum magnitude later than the negative cavity and subendocardial potentials. In normal hearts

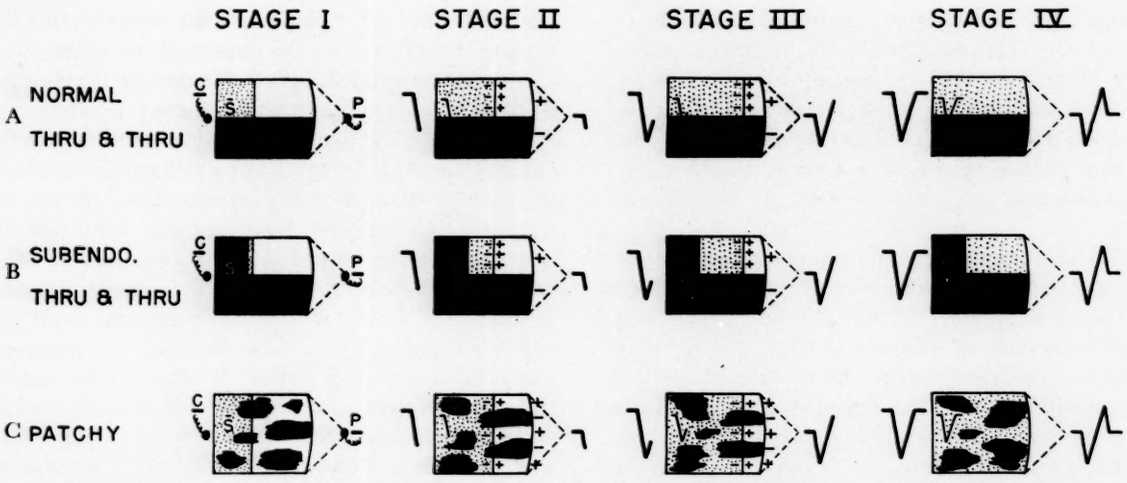


FIG. 9. Diagrams showing genesis of QR wave in precordial electrocardiogram. Infarcted muscle shown in black. Ventricular cavities to left of each diagram, epicardial surfaces to right. Electrode C is in cavity. Electrode S is at subendocardial level of wall. Electrode P is on precordium. Dotted lines indicate angle subtended by precordial electrode. Activation front is shown as series of dipoles, the positive pole preceding and the negative pole following the front. Clear areas correspond to resting (polarized) muscle ahead of activation front, stippled areas to depolarized muscle behind front. Stage I: Subendocardial depolarization. Stage II: Midventricular depolarization. Stage III: Late stage of depolarization. Stage IV: Completion of depolarization.

A, left ventricle containing transmural infarct bordered by live muscle. Electrode P subtends angle with both live and dead tissue. Stage I: Depolarization of the subendocardial layers is assumed to have no significant effect on the electrocardiogram. See text for explanation. All tracings, therefore, remain isoelectric. Stage II: Depolarization is now proceeding at recordable rates toward the epicardial surface. Portion of intramural activation front shown at boundary between polarized and depolarized muscle. Cavity and subendocardial electrodes face the negative side of the intramural activation front. These electrodes also face the negative side of the septal activation front (not shown in diagrams). Hence they record a negative potential, or Q wave. The negative potential is transmitted through dead subepicardial muscle to the overlying epicardial surface. Simultaneously, the surface over the live muscle is facing the positive side of the activation front. It therefore presents a positive potential. Since precordial electrode P subtends an angle with both live and dead muscle, it will record both the positive and the negative potentials. The positive potential is assumed to increase in magnitude relatively slowly because of a slowing of depolarization near the infarct. The negative potential thus exceeds the positive potential registered by electrode P, causing an initial negative deflection or Q wave in the precordial lead. Stage III: As the activation front approaches the surface, the positive potential increases in magnitude.[6] The negative potential, on the other hand, has already reached its maximum magnitude and is decreasing. Precordial electrode P registers both the increasing positive potential and the decreasing negative potential. When the positivity becomes stronger than the negativity, the upstroke of the R wave appears in the precordial leads. Stage IV: As the activation front reaches the epicardial surface, an intrinsicoid deflection occurs in the precordial tracing. The completed complex consists of a coronary QR wave.

B, left ventricle containing transmural infarct with subendocardial extension. Electrode positions same as in A. The angle subtended by the precordial electrode includes both live and dead muscle. Subendocardial portion of the infarct lies within the "electrocardiographically silent" zone. Hence it does not affect the depolarization complex. All tracings are therefore the same as in A. The precordial complex again consists of a QR wave.

C, a patchy infarct is present in the outer ventricular layers. Precordial electrode P subtends an angle with both live and dead muscle. Stage I: Depolarization of the inner layers does not affect the electrocardiogram. Tracings remain isoelectric regardless of the status of these layers. Stage II: The subendocardial and cavity electrodes record negative potentials as they face the negative side of the activation front. These negative potentials are transmitted through dead subepicardial muscle to the epicardial surface. At the same time, a positive surface potential develops over the live muscle which faces the positive side of the activation front. Since the precordial electrode is over both live and dead muscle, it records both the positive and negative potentials. As in A, the positivity is assumed to increase in magnitude more slowly than the negativity. Hence the precordial complex begins with a Q wave. Stage III: The activation front has traveled away from the cavity and subendocardial layers toward the epicardial surface. Thus the positive potential over the live muscle has become stronger while the negative potential transmitted through dead muscle has become weaker. Precordial electrode P again registers a summation of the positive and negative potentials. The resultant deflection is a gradual upstroke which crosses the baseline. Stage IV: As depolarization of the wall beneath the electrode ends, the precordial complex returns to the baseline. A coronary QR wave has been inscribed.

the cavity, subendocardial and surface potentials usually were found to achieve maximum magnitude almost simultaneously. The positive potential over ischemic muscle, on the other hand, may reach maximum magnitude relatively late, perhaps because the rate of depolarization is slowed. This observation was made during experimental studies on the immediate effects of coronary artery ligation to be reported elsewhere. Since the live muscle in Figure 9 is near or within an infarct, it has been assumed to undergo ischemic changes which delay the peak of the positive potential. Under such circumstances the negative potential registered by the precordial electrode would tend to exceed the positive potential early in depolarization (Stage II) while the reverse would be true later in depolarization (Stage III). Hence a precordial QR wave may occur.

2. Live and dead subepicardial muscle must be present in certain proportions in order to cause QR waves. If only a small amount of superficial muscle is dead, a Q wave would not be expected to appear. Conversely, if relatively little live muscle remains in the outer layers, an R wave may not occur.

3. Electrical activity in distant parts of the heart affects the precordial electrocardiogram.[7] These effects may prevent occurrence of a QR wave even when all conditions for the production of such complexes are fulfilled by the muscle facing the electrode.

In summary, both live and dead muscle may be present in the outer ventricular layers of hearts containing patchy infarcts, transmural infarcts adjacent to normal muscle, cone-shaped infarcts or, as is rarely seen, subepicardial infarcts. Whether or not such lesions yield QR waves would depend upon their location with respect to the recording electrode, upon their size and upon the proportion of live and dead muscle in the outer layers of the wall. QR deflections apparently do not occur if the subepicardial tissue is in its entirety, or almost in its entirety, alive or dead. Thus the coronary QR wave presumably is correlated with a balanced mixture of live and dead muscle in the outer layers and is relatively independent of the status of deeper levels of the wall.

The foregoing hypothesis appears consistent with the reported clinicopathologic data concerning coronary QR waves. In the majority of patients studied subendocardial infarction was demonstrated histologically beneath the sites from which precordial QR waves were obtained.[8–11] With few exceptions, however, histologic examinations also revealed variable amounts of dead tissue at superficial levels of the ventricle. It is suggested that the precordial Q wave resulted from involvement of the superficial muscle rather than from subendocardial infarction as hitherto supposed. This would explain why subendocardial infarcts were reported to yield QR waves in some patients[8,10,11] but not in others.[12] If significant amounts of infarcted muscle were present at superficial levels, the precordial electrode might face both live and dead subepicardial tissue. Hence a precordial QR wave could occur. If, on the other hand, the outer ventricular layers remained normal, the normal R wave resulting from activation of these layers would be expected to appear. This hypothesis can be tested by means of clinicopathologic studies on hearts presenting chronic infarcts. Patients with old lesions who die from other causes provide the most suitable subjects for postmortem cardiac study because the electrocardiographic and histologic changes have become stabilized.

Evaluation of the Depolarization Complex Following Coronary Artery Occlusion. The preceding discussion of precordial QR waves is based upon two theoretical concepts, both of which are supported by direct experimental evidence: (1) A positive potential (R wave) recorded over normal hearts results from depolarization of the outer ventricular layers. (2) A negative potential (Q or S wave) recorded over infarcts is transmitted through dead muscle. The first concept is derived from the observation that subendocardial infarcts limited to the inner half of the ventricular wall do not alter the normal R wave. Inactivation of the outer ventricular layers by various methods, on the other hand, causes the R wave to disappear or to become markedly smaller.[3a] Furthermore, R waves cannot be recorded in intramural leads from the inner layers but consistently appear in leads from the outer layers. The second concept was originally presented by Wilson[4,13] and has been confirmed by means of intramural leads from through-and-through infarcts.[3a] The negative cavity potential is transmitted through dead muscle to the ventricular surface, producing a coronary QS wave. By applying these two theoretical concepts it should be possible to explain other common types of depolarization complexes seen clinically following coronary artery occlu-

sion. Such explanations are subject to the same qualifications as the discussion of precordial QR waves. They are intended to illustrate general principles of electrocardiography in terms of two-dimensional muscle strips and can be applied only within certain limits to the interpretation of clinical electrocardiograms.

Subendocardial Infarction. After a typical coronary artery occlusion the clinical electrocardiogram shows characteristic changes in the S-T segment and T wave. These acute signs are commonly followed by evidence of infarction such as elevated sedimentation rate, high white cell count and fever. The depolarization complex, however, may be entirely normal in all leads. Despite the absence of QRS changes the patient cannot be assumed to have escaped infarction. Purely subendocardial lesions involving a large proportion of the ventricular myocardium may be present. Since such lesions do not involve the zone which produces the normal R wave, they would not alter the depolarization complex.

If the depolarization complex remains normal following a typical coronary artery occlusion, the outer ventricular layers which produce this complex presumably have not been damaged. Thus the presence of normal R waves in all leads would indicate that the outer layers of the ventricle remain intact. Restrictions designed to prevent cardiac rupture might therefore be relaxed since the ventricle is largely protected against this complication by a covering of intact muscle.

R Waves of Reduced Amplitude. The normal R wave is presumed to result from depolarization of the outer ventricular layers. A reduction in amplitude of the R wave thus must indicate that some cells in the outer layers fail to depolarize. Other cells in these layers remain active, thereby producing the small r wave. Under certain circumstances negative potentials may be transmitted from underlying regions through the inactive subepicardial cells to the recording electrode. The small r wave would then represent a summation of positivity relating to the active subepicardial cells and negativity transmitted through the inactive subepicardial cells.

Changes in size of the R wave following coronary artery occlusion sometimes cannot be recognized unless control electrocardiograms are available for comparison. This is exemplified by patients with hypertension who present abnormally large R waves over the left precordium owing to left ventricular hypertrophy. After repeated coronary attacks the amplitude of the R waves may be reduced as the outer ventricular layers which produce this deflection are extensively infarcted. Nevertheless, the remaining live muscle at superficial levels of the hypertrophied ventricle is sufficient to produce an R wave comparable to that recorded from patients with uninfarcted hearts of normal size.

Abnormal rS Waves. Abnormally small r waves followed by abnormally large S waves are a common finding in clinical coronary artery occlusion. These complexes may be explained by extending the hypothesis illustrated in Figure 9. As represented in the diagrams, a negative deflection (Q wave) is inscribed when the negative potential transmitted through dead subepicardial muscle is of greater magnitude than the positive potential resulting from depolarization of live subepicardial muscle. Conversely, a positive deflection (R wave) is recorded when the positive potential is greater than the transmitted negative potential. Abnormal rS waves thus would be expected to appear if the transmitted negative potential were of lesser magnitude than the positive potential early in depolarization, but were greater than the positive potential later in depolarization.

Theoretically, then, abnormal rS waves may be associated with the same pathologic picture as abnormal QR waves; namely, a mixture of live and dead muscle in the outer ventricular layers. If all other factors are constant, this type of lesion is most likely to yield abnormal rS waves over regions of the heart which depolarize early and abnormal QR waves over regions which depolarize relatively late. In regions which depolarize early the positive surface potential would tend to reach its greatest magnitude before the negative cavity potential is fully developed. The positivity resulting from activation of live subepicardial muscle thus is apt to exceed the negative potential transmitted through dead muscle early in depolarization, while the reverse would be true later in depolarization. Under such circumstances the resultant complex would be an abnormal rS wave. In regions which depolarize late, owing either to their location or to a slowing of transmural depolarization, the transmitted negative potential would tend to reach its maximum magnitude earlier than the positive surface potential. As shown in Figure 9, the resultant complex is then likely to be a QR wave.

"Mural-Type" QS Waves. As discussed elsewhere[3a] coronary QS waves may occur despite the presence of live muscle in the underlying wall. These so-called "mural-type" QS waves may be notched or slurred, or they may appear "pure." Like abnormal rS and QR waves, mural-type QS waves are associated with mixtures of live and dead muscle in the outer ventricular layers. The negative potential transmitted through the dead muscle exceeds the positive potential contributed by the remaining live subepicardial muscle throughout the period of depolarization. Hence the positivity is "buried" in the negativity. The resultant complex consists of an entirely negative deflection, or QS wave.

"Cavity-Type" QS Waves. These complexes, originally described by Wilson,[4] consist of pure negative deflections identical with the QS wave recorded from the underlying ventricular cavity. Cavity-type QS waves occur over through-and-through infarcts in which the entire thickness of the wall, from endocardium to epicardium, is completely dead.[3a] Since no live muscle is present in the outer layers, no positive potential (R wave) is produced. The negative cavity potential is therefore transmitted unaltered to the electrode.

Transient Changes in the Depolarization Complex. Marked alterations in the depolarization complex associated with clinical coronary artery occlusion occasionally disappear after the attack. Normal R waves may recur, replacing abnormal QS, QR or rS waves. In such instances the outer ventricular layers presumably were temporarily inactivated but were not irreparably damaged by the occlusion. As circulation improved these layers healed sufficiently to resume normal activity, thereby restoring the R waves.

From the foregoing discussion it is apparent that the presence of both live and dead muscle in the outer ventricular layers may yield a variety of abnormal depolarization complexes including small r waves, rS waves, QR waves and "mural-type" QS waves of diverse sizes and contours. Each of these abnormal complexes represents a summation of two potentials: a positive surface potential of reduced magnitude resulting from activation of the remaining live subepicardial muscle, and a negative potential transmitted to the surface through dead subepicardial muscle. If the outer layers remain intact, as in the normal heart and in purely subendocardial infarction, a positive potential of normal magnitude is recorded; hence a normal R wave occurs. If the outer layers are completely inactivated, as in through-and-through infarction, only the transmitted negative potential is recorded; a pure QS wave then occurs. If both the positive and the negative potentials are recorded, the configuration of the resultant complex will depend upon the relative magnitude and timing of the reduced surface positivity as compared with the transmitted negativity. Abnormally small r waves appear when the magnitude of the positive potential is greater than that of the transmitted negative potential throughout depolarization. Conversely, mural-type QS waves occur when the transmitted negativity is greater than the positivity throughout depolarization. QR waves appear when the transmitted negativity is of greater magnitude than the positivity early in depolarization but is less than the positivity later in depolarization. Finally, abnormal rS waves appear when the positivity exceeds the transmitted negativity early in depolarization but the negativity exceeds the positivity later in depolarization.

That a mixture of live and dead subepicardial muscle may be associated with various types of QRS abnormalities has been confirmed in the present experimental study. Of the twenty-three infarcts from which surface QR waves were recorded, the majority presented abnormally small r waves, abnormal rS waves and/or mural-type QS waves in surface leads from different sites. Thirty-eight other infarcts produced by coronary artery ligation also exhibited a variety of abnormal surface complexes ranging from small r waves to QS waves. Histologic examination established that all the sites which yielded small r waves, abnormal rS waves, QR waves or mural-type QS waves were located directly over or near both live and dead subepicardial muscle. It appears reasonable to suppose that some correlation would exist between the amount of dead muscle in the outer ventricular layers and the degree of change in the surface depolarization complex. Although this problem was not thoroughly studied, the impression prevailed that mural-type QS waves were associated with a somewhat greater amount of subepicardial muscle death than were QR waves or abnormal rS waves.

If the preceding theoretical considerations apply clinically, prevailing criteria for the interpretation of electrocardiograms following coronary artery occlusion may need revision. When the depolarization complex remains

normal after signs of acute occlusion, the presence of a pure subendocardial infarct must be suspected. Contrary to classic theory, such lesions would not yield coronary QR waves. On the other hand, any significant change in the depolarization complex must be assumed to result from involvement of the outer ventricular layers. Abnormally small r waves, abnormal rS waves, QR waves and mural-type QS waves indicate that the outer ventricular layers contain variable mixtures of live and dead muscle. QS waves also may occur when the entire thickness of the wall beneath the electrode is dead. Finally, the configuration of the depolarization complex does not provide information concerning the status of the inner ventricular layers. Essentially similar complexes will be recorded whether the inner layers are wholly intact, partially infarcted or all dead. It is hoped that these comments on the interpretation of the depolarization complex will help to clarify the relationship between electrocardiographic and pathologic changes following coronary artery occlusion. As this relationship is better understood, the diagnostic value of the clinical electrocardiogram will be greatly increased.

CONCLUSIONS

Electrocardiographic and histologic data were correlated in a series of sixty-eight infarcts produced in dogs by coronary artery ligation. Contrary to classic theory, pure subendocardial lesions did not yield coronary QR waves. An attempt was therefore made to determine the circumstances under which coronary QR waves do occur.

Twenty-six QR waves recorded in direct surface leads from twenty-three infarcts were analyzed. At superficial levels of the ventricle some fibrotic muscle was always found directly beneath or adjacent to the QR lead-points. As shown by injury currents variable amounts of live muscle also were always present immediately beneath the electrode. A mixture of live and dead muscle in the outer ventricular layers was therefore associated with coronary QR waves. Hypotheses are presented to explain why this pathologic situation may yield QR waves in precordial leads.

Subendocardial muscle directly beneath the twenty-six QR lead-points varied histologically from completely normal to wholly dead. Thus the occurrence of coronary QR waves was independent of the status of the deeper ventricular layers.

Previous clinicopathologic studies have yielded conflicting results concerning the genesis of coronary QR waves. Patients with subendocardial infarcts were found to show precordial QR waves in some instances and normal R or Rs waves in other instances. The following explanation of these varying results is suggested. Pure subendocardial infarcts do not alter the QRS complex in precordial electrocardiograms. Ventricles containing subendocardial lesions with some involvement of the superficial layers may yield precordial QR waves. The QR wave is not correlated with the subendocardial infarction. Rather, it occurs when the superficial layers contain both live and dead muscle.

An explanation of the various types of QRS changes seen clinically after coronary artery occlusion is presented. Death of muscle in the outer ventricular layers eliminates or reduces the magnitude of the positive epicardial potential (R wave). Negative potentials (Q or S waves) transmitted through the dead subepicardial muscle further alter the depolarization complex. A mixture of live and dead muscle in the outer ventricular layers thus may result in a variety of QRS changes including abnormally small r waves, abnormal rS waves, QR waves and QS waves of various sizes and shapes. Which type of complex occurs depends upon the relative magnitude and timing of the reduced positive epicardial potential and the transmitted negative potential.

Practical aspects of the interpretation of clinical electrocardiograms following coronary artery occlusion are discussed. The diagnostic value of these tracings can be increased as the relationship between electrocardiographic and histologic changes is more fully understood.

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Metabolism of the Human Heart*

II. Studies on Fat, Ketone and Amino Acid Metabolism

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Results described in a previous paper of this series dealing with the carbohydrate metabolism of the human heart indicated that the total aerobic metabolism of glucose, lactate and pyruvate combined fell short of the total oxygen consumption of the heart.[1,2] This suggested that the heart also used non-carbohydrate substances for provision of its energy. Previous work on the heart-lung preparation pointed in this direction. Evans, for example, has shown that when animals are fed a diet consisting largely of butter the respiratory quotient of the isolated heart is low.[3] Evans and Matsuoka,[4] Ruhl[5] and Bogue and co-workers[6] found that under certain conditions cardiac oxygen consumption could be accounted for only partly by combustion of carbohydrate materials. Visscher and Mulder compared the myocardial carbohydrate extraction to the oxygen consumption of the isolated heart and found that as much as 80 per cent of the total metabolism may be derived from some energy source other than carbohydrate.[7] Since they found no evidence of increase in non-protein nitrogen, they concluded that fat must have been burned.[7] Bayliss, Muller and Starling reported that the R.Q. of the heart-lung preparation is below 0.95 and is probably considerably less.[8] Cruickshank and Kosterlitz, by analysis of fatty acids in heart muscle and blood perfusates, concluded that cardiac fat was replenished from blood fatty acids and that the source of cardiac energy, insofar as it is derived from fat, is the blood fatty acids.[9] However, these authors were of the opinion that utilization of fatty acids may not occur regularly since they found fat utilization only in the presence of an acute shortage of carbohydrates.[9]

Along with fatty acids, ketone bodies appear to be utilized by the isolated heart muscle. Barnes and his associates found that heart muscle can utilize beta-hydroxybutyric acid.[10] Waters et al. in studying the problem of a possible ketolytic action of glucose discovered that ketone bodies were utilized by the heart-lung preparation.[11] There was no evidence of any definite ratio between utilization of carbohydrates and acetone bodies, indicating that oxidation of ketones is not dependent on carbohydrate oxidation. There has thus been general agreement as to the usage of fats and ketones by the isolated heart.

Little work has been published on the myocardial consumption of amino acids. Cruickshank and McClure examined this problem in the heart-lung preparation, using ammonia formation as indication of deamination of amino acids.[12] They concluded that neither naturally occurring amino acids nor those not occurring in nature are utilized by the heart. It is quite possible, however, that their failure to detect ammonia resulted from the fact that it did not remain free in blood, most of it having been taken up by glutamic acid to form glutamine.

It is the purpose of this communication to study the utilization of fats, ketones and amino acids by the human heart, and to compare the oxygen utilized in the aerobic metabolism of these substances to the oxygen uptake of the heart.

TECHNICAL AND THEORETICAL CONSIDERATIONS

Most of the methods used in this investigation have been described in detail in preceding communications of this series.[1,2] Coronary vein blood was obtained by direct intubation of the coronary sinus.[13] The coronary flow was measured in five patients with the nitrous oxide method.[14] Mixed venous blood was obtained from the pulmonary artery or the right ventricle for calculation of the cardiac output by the

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Fick principle.[15] Pulse rate, stroke volume, mean blood pressures and left ventricular work were determined as previously described.[14] Blood glucose was determined by the method of Hagedorn and Jensen[16] using Somogyi's method to prepare the blood filtrates.[17] Pyruvate was determined according to the method of Friedemann and Haugen, using a trichloracetic acid filtrate.[18] Lactate was measured by the method of Barker and Summerson.[19] The manometric method of Van Slyke and Neill was used for blood oxygen analyses.[20] Fatty acids were determined according to the method of Man and Gildea.[21] This is essentially a modification of the procedure of Stoddard and Drury's volumetric method.[22] The maximum calculated error of this method is ± 5.0 per cent.[21] Amino acids were measured according to the procedure of Albanese and Irby.[23] This copper amino nitrogen method has the advantage of great accuracy (better than 1 per cent) and of rapidity of operation. Ketones were determined by a modification of the micromethod of Greenberg and Lester.*[24]

The myocardial usage of carbohydrates, fats and proteins per 100 gm. of heart was estimated as the product of coronary flow/100 gm. of cardiac muscle times the respective myocardial oxygen, glucose, lactate, pyruvate, fatty acid, amino acid and ketone extractions. The oxygen extraction ratios of these individual energy sources were calculated as the ratios of their oxygen equivalent to the myocardial oxygen extraction;† the oxygen extraction ratio represents the contribution of the aerobic catabolism of these substances to the total myocardial oxygen extraction.[1] Excluding the possibility of storage or conversion of foodstuffs within the metabolic pool, an elevation of the oxygen extraction ratio of an individual metabolite indicates that a large proportion of oxidative energy is used in the aerobic metabolism of this substance. Conversely, if there is a decrease in the oxygen extraction ratio, a smaller proportion of oxygen taken up by the heart is used in the aerobic metabolism of this compound. However, because of the possibility of both storage and conversion, alterations in the oxygen extraction do not necessarily indicate a change in the amount of oxygen utilized in the metabolism of these foodstuffs. Oxidation of foodstuffs to carbon dioxide and water for the provision of energy is not the sole factor in determining the myocardial extraction of these compounds. For example, an increase in myocardial glucose extraction may be the result of its conversion into glycogen. Since this is a strictly aerobic process, the oxygen extracted from the coronary blood would be used for storage and not for chemical energy. The increase in the oxygen extraction ratio of fat does not necessarily imply an increase in the proportion of oxygen used by the heart in the aerobic metabolism of fat; there may also be storage of fat by the heart. This is particularly likely if the oxygen extraction ratio of fatty acids is above 100 per cent, as is often the case after a high fat intake. Although the methods described in this report permit certain assumptions as to the manner in which the heart muscle handles its metabolic fuel, they do not permit any definite conclusions as to the metabolic pathway within the heart muscle cell; only over-all results of these intermediary processes become apparent.

The tests were carried out on a total of thirty-three patients. None of these were in cardiac failure. As indicated in Tables I, II and III, several subjects tested had no evidence of heart disease; the remainder had hypertensive, rheumatic, arteriosclerotic or congenital heart disease. The effect of high fat intake was studied in eight patients. (Table II.) In these individuals food was withheld for twelve hours prior to the oral administration of 2 ounces of a fat emulsion containing 19 per cent saturated and 81 per cent unsaturated fatty acids.* Studies were then carried out from three to four hours after ingestion of this preparation. The effect of infusion of a protein hydrolysate containing a high percentage of amino acids was investigated in six patients. (Table III.) Following sampling of arterial and coronary vein blood for control determinations, the protein hydrolysate† was infused intravenously at a rate of 60 drops per minute. Samples were then drawn ten and twenty minutes from the onset of the infusion.

* We are grateful to Dr. Frank Engel of the Department of Medicine, Duke University for his advice in the determination of ketones.

† The oxygen equivalents were calculated as follows: Glucose: myocardial glucose extraction (mg. %) times 0.75; pyruvate: myocardial pyruvate extraction (mg. %) times 0.64; lactate: myocardial lactate extraction (mg. %) times 0.75; fatty acids: myocardial fatty acids extraction (mEq.) times 570; ketones: myocardial ketone extraction (mg. %) times 1.02; amino acids: myocardial amino acid extraction (mg. % nitrogen) times 4.68.

* Lipomul, Upjohn Company.

† Aminosol, Abbott Laboratories.

TABLE I

Patients	Diagnoses	Cardiac Index (L./M²)	Left Ventricular Work (kg./met.)	R.Q. of Heart	Coronary Flow (cc./100 gm./min.)	Myocardial Extractions									
						Oxygen (vol. %)	Arterial Glucose (mg./100)	Δ Glucose (mg./100)	Arterial Pyruvate (mg./100)	Δ Pyruvate (mg./100)	Arterial Lactate (mg./100)	Δ Lactate (mg./100)	Arterial Fatty Acids (mEq./100)	Δ Fatty Acids (mEq./100)	Arterial Amino Acids (mg. N_2/100)
1. C. I.	R.H.D., M.I., M.S.	5.16	11.7	0.5	.....	6.8	95.3	1.0	0.338	0.047	7.1	1.08	.....	.....	4.80
2. B. F.	H.C.V.D.	3.24	7.63	0.9	.....	8.3	88.6	3.1	0.54	0.08	9.34	0.99	0.890	0.0035	4.20
3. W. W.	A-V fistula, lung	4.3	8.0	0.85	.....	8.6	82.6	5.1	0.423	0.05	13.95	4.49	0 605	0.010	5.03
4. E. T.	H.C.V.D.	3.75	7.9	0.75	77	10.1	93.2	1.0	0.245	0.141	8.30	3.4	1.470	0.003	3.54
5. W. W.	Cor pulmonale	3.93	7.8	0.80	....	8.6	95.7	2.4	0.472	0.075	14.30	3.3	1.165	0.040	4.45
6. E. T.	R.H.D., M.S.	4.4	9.9	0.52	.....	10.3	101.1	3.3	0.365	0.125	4.92	1.11	0.88	0	4.75
7. J. S.	C.H.D.	2.6	.....	0.73	....	11.2	81.4	1.4	0.511	0.044	13.1	2.5	.....	0	5.59
8. B. C	C.H.D.	5.7	.....	0.77	.....	11.6	90.2	3.0	0.683	0.105	7.18	1.9	0.950	0.004	8.75
9. O. B.	Cor pulmonale	5.5	11.8	0.78	.....	11.2	104.2	3.0	0.480	0.120	4.70	0.26	1.12	0.017	3.66
10. L. I.	H.C.V.D.	2.8	6.6	0.62	85	12.2	74.0	2.0	0.503	0.121	8.53	2.33	1.58	0.021	3.80
11. A. E.	H.C.V.D.	5.6	22.5	0.69	.....	11.0	89.1	1.8	0.592	0	5.13	1.63	0.870	0.044	3.58
12. H. W.	Normal	3.9	9.0	0.93	.....	10.2	110.5	2.0	1.02	0.08	7.0	0.30	1.76	0.015	8.50
13. A. R.	Normal	4.2	6.0	1.0	.....	9.64	85.0	.40	0.727	0.184	7.25	2.17	0.920	0.043	8.14
14. W. T.	Cor pulmonale	4.2	6.8	.....	.....	8.60	90.4	1.30	1.370	0.190	11.08	0.31	0.870	0.013	9.0
15. T. D.	A-V fistula	3.7	8.2	0.75	74	13.3	90.8	5.40	0.928	0.208	7.16	2.29	1.042	0.002	4.22
16. S. I.	A-V fistula	5.1	6.8	0.68	.....	10.9	105.2	2.0	0.462	.....	7.94	3.27	1.060	0.018	4.35
17. J. A.	H.C.V.D.	2.5	5.6	0.94	92	9.0	.....	.....	.....	.....	.....	.....	1.073	.....	10.92
18. E. M.	H.C.V.D.	3.2	8.9	0.73	.....	10.8	.....	.....	.....	.....	.....	.....	0.910	0.014	3.33
19. C. G.	H.C.V.D.	4.3	9.6	0.62	.....	15.2	91.0	4.5	0.58	0.11	5.5	2.3	1.555	0.015	5.25
20. D. A.	Normal	4.4	8.6	0.74	.....	12.5	90.2	4.8	0.376	0.019	8.10	4.03	1.135	0.0075	4.40
21. V. G.	Hyperthyroid	4.6	10.1	0.41	.....	11.5	87.2	4.7	0.328	0.058	9.77	2.20	1.276	0.021	14.1
22. E. H.	H.C.V.D.	2.33	6.7	0.73	90	11.9	86.1	1.1	0.339	0.034	5.87	2.51	0.985	0.030	3.96
No. of Observations	.....	22	20	21	5	22	20	20	19	20	20	20	20	20	22
Mean	.....	4.050	9.034	0.690	83.6	10.610	91.59	2.665	0.564	0.094	8.311	2.19	1.105	0.016	5.423
Range	.....	5.7/2.3	22.5/5.6	1.0/0.5	92/74	15.2/6.8	110.5/74	5.4/0.4	1.370/0.328	208/0	14.30/5.5	4.49/.26	1.76/0.605	0.043/000	14.1/3.33
Standard deviation	.....	1.02	3.50	2.92	6.93	1.849	7.84	1.49	0.272	0.051	2.803	1.92	0.286	0.013	3.054
Coefficient of variation	.....	.....	.....	.....	.....	17.0%	8.4%	55%	48%	54%	34%	90%	26%	81%	56%

TABLE I (*Continued*)

Patients	Myocardial Extractions			Myocardial Usages—(100 gm./minute)							Oxygen Extraction Ratio						Oxygen Extraction Ratio (%)	
	Δ Amino Acids (mg./N_2/100)	Arterial Ketones (mg./100)	Δ Ketones (mg./100)	Oxygen (cc.)	Glucose (mg.)	Pyruvate (mg.)	Lactate (mg.)	Fatty Acids (mEq.)	Amino Acids (mg./N_2)	Ketones (mg.)	Glucose	Pyruvate	Lactate	Fatty Acids	Amino Acids	Ketones	Total Carbohydrates	Total Noncarbohydrates
1. C. I.	0.36	2.28	0.71	.....	.....	.....	.....	.....	.....	.....	11.1	0.47	12.4	.....	26.0	10.4	23.9	36.4
2. B. F.	0.05	1.57	0.635	.....	.....	.....	.....	.....	.....	.....	28.0	0.60	9.0	16.0	3.0	7.6	34.6	29.6
3. W. W.	0.03	0.364	0.137	.....	.....	.....	.....	.....	.....	.....	32.0	0.27	39.0	0	2.0	1.6	71.0	3.6
4. E. T.	0.12	1.92	0.23	7.8	0.77	0.18	2.61	0.002	0.09	0.17	7.4	0.88	25.5	15.0	6.0	2.3	33.8	23.3
5. W. W.	0.160	0.755	0.212	.....	.....	.....	.....	.....	.....	.....	21.0	0.50	29.0	.....	9.0	2.4	50.5	11.4
6. E. T.	0	1.07	0.357	.....	.....	.....	.....	.....	.....	.....	24.0	0.80	8.0	0	0	3.4	32.8	3.4
7. J. S.	0.04	1.82	0.550	.....	.....	.....	.....	.....	.....	.....	9.5	0.22	16.7	0	2.0	4.9	26.4	6.9
8. B. C.	0.45	2.02	0.610	.....	.....	.....	.....	.....	.....	.....	19.4	0.50	13.0	17.0	18.0	5.0	31.9	40.0
9. O. B.	0.05	1.48	0.675	.....	.....	.....	.....	.....	.....	.....	20.0	0.60	1.7	79.0	2.1	7.6	22.3	88.7
10. L. I.	0.05	1.67	0.380	10.4	1.70	0.10	1.9	0.02	0.04	0.33	12.3	0.60	14.2	89.0	1.9	3.1	27.1	94.0
11. A. E.	0.08	2.04	0.570	.....	.....	.....	.....	.....	.....	.....	12.2	0	11.1	208.0	3.5	5.2	23.3	216.7
12. H. W.	0.09	1.35	0.857	.....	.....	.....	.....	.....	.....	.....	14.6	0.41	2.0	78.0	4.3	8.0	17.0	90.3
13. A. R.	0.44	0.654	0.184	.....	.....	.....	.....	.....	.....	.....	3.0	1.2	16.9	230.0	.....	1.9	21.1	231.9
14. W. T.	0.05	1.92	0.660	.....	.....	.....	.....	.....	.....	.....	11.3	1.38	2.7	78.0	2.8	7.7	15.4	88.5
15. T. D.	0.10	0.895	0.469	9.9	4.0	0.15	1.7	0.001	0.07	0.35	31.0	1.0	40.0	7.5	3.6	3.5	72.0	14.6
16. S. I.	0.17	1.39	0.495	.....	.....	.....	.....	.....	.....	.....	13.8	.....	22.7	85.0	7.6	4.6	36.5	97.2
17. J. A.	0	0.30	0.06	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....
18. E. M.	0.01	0.72	0.06	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	66.0	0.47	0.55	.....	.....
19. C. G.	0.20	1.68	0.36	.....	.....	.....	.....	.....	.....	.....	22.0	0.46	11.2	49.0	6.4	2.3	33.66	57.7
20. D. A.	0.07	0.625	0.305	.....	.....	.....	.....	.....	.....	.....	29.0	0.09	24.0	33.0	2.7	2.5	53.09	38.2
21. V. G.	0.40	1.36	0.08	.....	.....	.....	.....	.....	.....	.....	30.8	0.28	14.3	94.0	17.0	0.69	45.38	111.69
22. E. H.	0	3.79	0.69	10.7	0.9	0.03	2.28	0.03	0	0.62	6.8	0.18	15.8	130	0	5.9	22.8	136
No. of Observations	22	22	22	4	4	4	4	4	4	4	20	19	20	19	20	21	20	20
Mean	0.132	1.440	.422	9.70	1.842	.115	2.122	.013	.05	.37	17.96	0.549	16.46	67.236	5.63	4.34	34.876	76.004
Range	0.45/0	3.79/0.3	0.857/0.06	10.7/7.8	4.0/0.77	0.18/0.03	2.61/1.7	0.072/0.001	0.09/0	0.62/0.055	32/6.8	1.38/0	40.2	208/0	26/0	10.4/.55	72/15.4	231.6/34
Standard deviation	.1667	.770	.234	1.174	1.30	.0548	.36	.005	.03	.16	8.77	.295	12.06	64.21	6.91	3.07	15.76	64.25
Coefficient of variation	127%	53%	55%	12.3%	72%	48%	17%	38%	60%	26%	48%	54%	73%	96.0%	123%	72%	45%	90%

C.H.D. = Congenital heart disease.
H.C.V.D. = Hypertensive cardiovascular disease.
R.H.D. = Rheumatic heart disease.
M.S., M.I. = Mitral stenosis; mitral insufficiency.

In one patient (E. L. H., Table III) the second sample was drawn thirty minutes after beginning the infusion. In all instances, coronary vein and peripheral arterial blood were sampled simultaneously.

RESULTS

In addition to extracting carbohydrates, the human heart extracts a considerable amount of

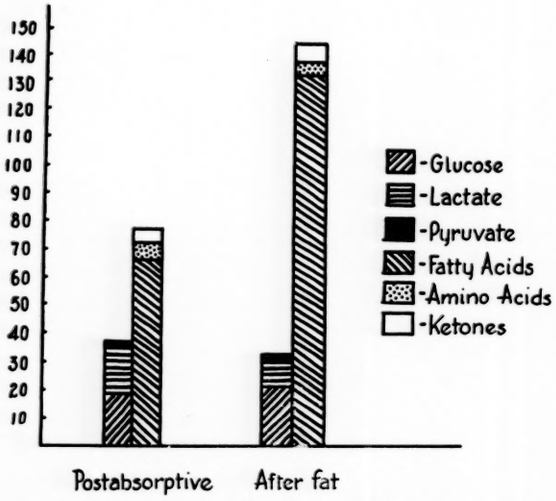


FIG. 1. Comparison of the myocardial oxygen extraction ratio of carbohydrate and non-carbohydrate foodstuffs in the postabsorptive state and after ingestion of fatty acids. Alimentary lipemia results in a considerable increase in the oxygen extraction ratio of fatty acids.

fatty acids. (Table I.) At blood fatty acid levels of from 0.605 to 1.76 mEq. per cent (mean 1.105 with a standard deviation of 0.286) the extraction of fatty acids ranged from 0 to 0.043 mEq. per cent with a mean of 0.016 and a standard deviation of 0.013; the scatter is therefore considerable. In most individuals in the postabsorptive state the oxygen extraction ratio of fatty acids was below 100 per cent, with an average of 67 per cent and a range from 0 to 208 per cent. The standard deviation was 64.2, demonstrating the large scatter of these observations. In three patients (A. R., G. V. and E. M. H., Table I) the oxygen extraction ratios of fatty acids were above 100 per cent. This observation suggests storage of fat by the heart.

The capacity of the heart to utilize fatty acids was further investigated in eight patients in whom studies were carried out three to four hours after the ingestion of 2 ounces of lipomul. As shown in Table II, high fat intake resulted in an apparent increase in myocardial extraction of fatty acids, ranging from 0.013 to 0.07 mEq. per cent with a mean of 0.028 and a standard deviation of 0.62. The myocardial usage of fatty acids in patient L. S. was 0.02 mEq. per cent of fat/100 gm. heart muscle/minute. Although the increase in fatty acid uptake was not statistically significant (1.3 x a S.E. of .0027), the rise in oxygen extraction ratio of fat was significant (2.3 x a S.E. of 27.6). The mean non-carbohydrate oxygen extraction ratios were also significantly greater than those of carbohydrates (2.3 x S.E. 27.9). The over-all average ratio between non-carbohydrate and carbohydrate oxygen extraction ratio was 4.6/1 whereas in the postabsorptive state this ratio was only 2.0/1. (Fig. 1.) It is likely that the high oxygen extraction ratio of fatty acid and the increase in the total non-carbohydrate fraction observed after fat ingestion were the result of combined oxidation and storage of fat in the myocardium. Storage is particularly suggested by the observation that the fatty acid oxygen extraction ratios exceeded 100 per cent in four of seven patients who had received lipomul. (Table II.) It had been found previously that the isolated heart can utilize fatty acids;[7,9] usage of fat by skeletal muscle had been demonstrated, among others, by Richardson, Shorr and Loebel who found that the average respiratory quotient of muscular tissue taken from depancreatized dogs was 0.70 to 0.75.[25] Storage of fat in heart muscle had been demonstrated experimentally by Wegelin who showed that following a fatty meal there was deposition of fat in the heart muscle.[26] Marked depositions of fat were also observed in hearts of dogs sacrificed three hours after ingestion of 3 ounces of lipomul.[27]

Ketone blood levels observed in patients in the postabsorptive state ranged from 0.36 to 3.79 mg. per cent, with an average of 1.4 mg. per cent and a standard deviation of 0.77. (Table I.) Similar values for blood ketones were found by Greenberg and Lester and by Weichselbaum and Somogyi.[24,28] The ketone extraction of the heart varied from 0.06 to 0.85 mg. per cent, with an average of 0.42 mg. per cent and a standard deviation of 0.23. (Table I.) In the four patients in whom myocardial usage of ketones was determined there was a range of from 0.05 to 0.62 mg./100 gm. of heart/minute, with a mean of 0.37 and a standard deviation of 0.16. The oxygen extraction ratios for ketone ranged from 0.55 to 10.4 per cent, with a mean of 4.3 and a standard deviation of 3.1. It is

TABLE II
INGESTION OF LIPOMUL

Patients	Diagnosis	Arterial Blood Levels and Myocardial Extractions												
		Oxygen (vol. %)	Arterial Glucose	Δ Glucose (mg./100)	Arterial Pyruvate	Δ Pyruvate (mg./100)	Arterial Lactate	Δ Lactate (mg./100)	Arterial Fatty Acids	Δ Fatty Acids (mg./100)	Arterial Amino Acids (mg./N_2/100)	Δ Amino Acids (mg./N_2/100)	Arterial Ketones	Δ Ketones (mg./100)
1. J.A.	M.S.	15.2	92.5	7.8	0.423	0.065	7.33	1.80	1.243	0.073	4.15	0.15	0.23	0.23
2. R. S.	M.S., C.H.F.	7.4	97.8	2.5	0.417	0.019	8.62	1.74	0.948	0.013	3.70	0.06	1.79	0.11
3. V. W.	Diabetes	14.0	140.6	1.6	0.445	0.063	9.72	2.10	1.653	0.04	3.28	0.25	2.64	0.94
4. E. M. J.	Collagen Disease	11.9	93.6	3.8	0.536	0.132	10.29	2.03	.....	.....	2.62	0.06	3.82	0.98
5. L. S.	Posthem-morhage anemia	6.5	106.2	0.2	0.454	0.098	4.46	0.39	1.040	0.020	3.38	0.05	3.78	0.82
6. J. B.	Cardiac infarction	10.1	94.5	0.2	0.450	0.097	5.12	1.18	1.077	0.022	3.75	0.07	0.975	0.14
7. J. W.	Hyperten.	11.8	100.0	5.5	0.310	0.38	5.26	0.63	1.216	0.016	4.35	0.10	4.76	0.26
8. R. C.	A.S.H.D.	8.2	97.4	2.7	0.302	0.061	6.58	2.25	1.380	0.015	3.64	0.02	3.25	0.53
Mean		10.64	102.82	3.04	0.417	0.071	7.172	1.52	1.272	0.028	3.608	0.095	2.66	0.501
Range		15.2/6.5	140.6/92.5	7.8/1.2	0.536/0.302	0.132/0.019	10.29/4.46	2.25/0.39	1.653/0.948	0.073/0.013	4.35/2.62	0.25/0.02	4.76/0.23	0.98/0.11
Standard deviation		2.92	14.87	244	0.072	0.036	2.07	0.64	0.213	0.62	0.5	0.071	1.442	0.342
Coefficient of variation (%)		22.5	14.1	80.0	5.8	51.0	29.0	42.0	17.5	71.5	13.8	75.0	54.0	68.0

Patients	Myocardial Usage (100 gm./min.)								Oxygen Extraction Ratio (%)						Oxygen Extraction Ratio	
	Coronary Flow	Oxygen (cc.)	Glucose (mg.)	Pyruvate (mg.)	Lactate (mg.)	Fatty Acids (mEq.)	Amino Acids (mg./N_2)	Ketones (mg.)	Glucose	Pyruvate	Lactate	Fatty Acids	Amino Acids	Ketones	Carbo-hydrate	Non-carbo-hydrate
1. J. A.	..	...	....	....	....	....	....	....	38.3	0.273	8.9	249.0	4.7	1.6	47.4	255.3
2. R. S.	..	...	....	....	....	....	....	....	25.3	0.165	17.5	91.0	3.9	1.5	42.9	96.4
3. V. W.	..	...	....	....	....	....	....	....	8.6	0.288	11.2	147.0	8.6	6.7	20.0	162.3
4. E. M. J.	..	...	....	....	....	....	....	....	23.9	0.710	12.8	.....	2.4	8.2	37.4	.....
5. L. S.	81	5.3	0.16	0.07	0.31	0.02	0.04	0.67	2.3	0.97	4.5	160.0	3.7	12.6	7.8	176.3
6. J. B.	..	...	....	....	....	....	....	....	1.5	0.65	8.8	112.0	3.36	1.4	10.9	116.8
7. J. W.	..	...	....	....	....	....	....	....	35.0	0.21	4.0	68.0	4.10	2.2	39.2	74.3
8. R. C.	..	...	....	....	....	....	....	....	24.5	0.47	20.6	95.0	1.19	6.5	45.6	102.7
Mean	..	...	....	....	....	....	....	....	19.92	0.467	11.04	131.71	3.98	5.09	31.4	140.58
Range	..	...	....	....	....	....	....	....	38.3/1.5	0.97/0.165	20.6/4.0	249/68.0	8.6/1.19	12.6/1.4	47.4/7.8	255.3/73.4
Standard deviation	..	...	....	....	....	....	....	....	13.28	0.267	5.91	56.38	2.05	3.86	11.65	57.65
Coefficient of variation (%)	..	...	....	....	....	....	....	....	67.0	57.0	53.5	43.0	51.5	76.0	37.0	39.3

TABLE III
INFUSION OF AMINOSOL

Patients	Diagnosis	Time (min.)	Arterial Blood Levels and Myocardial Extractions												
			Oxygen (vol. %)	Arterial Glucose	Δ Glucose (mg./100)	Arterial Pyruvate	Δ Pyruvate (mg./100)	Arterial Lactate	Δ Lactate (mg./100)	Arterial Fatty Acids	Δ Fatty Acids (mEq./100)	Arterial Amino Acids (mg./N₂/100)	Δ Amino Acids (mg./N₂/100)	Arterial Ketones	Δ Ketones (mg./100)
1. A. E.	Essential hypertension	Control	11.0	89.1	1.8	0.59	0	5.13	1.63	0.870	0.044	3.58	0.08	2.04	0.57
		10	.....	87.2	3.4	0.65	0.27	4.2	1.36	0.818	0.028	4.53	0.45	2.24	0.75
		20	.....	83.6	5.3	0.69	0.11	3.79	0.90	0.840	0.007	4.58	0.30	1.54	0.49
2. J. A.	Essential hypertension	Control	9.0	.....	.....	.....	.....	.....	.....	.....	.....	10.92	0	0.30	0.06
		10	.....	.....	.....	.....	.....	.....	.....	.....	.....	11.4	0.60	0.95	0.08
		20	.....	.....	.....	.....	.....	.....	.....	.....	.....	12.0	0.16	0.45	0.33
3. M. L. C.	Essential hypertension	Control	10.8	.....	.....	.....	.....	.....	.....	0.910	0.014	3.3	0.01	0.72	0.06
		10	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	0.27	0.15
		20	.....	.....	.....	.....	.....	.....	.....	0.872	0.042	4.62	0.02	0.72	0.45
4. D. A.	Ca. of stomach	Control	12.6	90.2	4.8	0.38	0.02	8.1	4.03	1.13	0.008	4.40	0.07	0.625	0.31
		10	.....	94.7	6.4	0.38	0.05	8.4	3.8	.....	.....	.....	.....	0.54	0.26
		20	.....	96.2	6.9	0.39	0.03	8.5	3.40	1.22	0.023	5.81	0.14	0.600	0.20
5. V. G.	Hyperthyroidism	Control	11.6	87.2	4.7	0.33	0.06	9.77	2.20	1.27	0.021	14.1	0.40	1.36	0.08
		10	.....	86.3	5.8	0.32	0.03	8.13	2.12	.....	.....	.....	.....	1.31	0.08
		20	.....	89.4	7.1	0.35	0.04	7.85	1.43	1.23	0	16.05	0.95	1.60	0.21
6. E. L. H.	H.C.V.D.	Control	11.9	86.1	1.1	0.339	0.034	5.87	2.51	0.985	0.030	3.96	0	3.79	0.69
		30	11.8	96.5	5.3	0.356	0.025	4.5	1.27	0.943	0.008	6.27	0.27	2.10	0.39
Control		Range	12.6/9	90.2/86.1	4.8/1.1	0.59/0.33	0.06/0	9.77/5.13	4.03/1.63	1.27/0.87	0.044/0.0075	14.1/3.3	0.40/0	3.79/0.3	0.69/0.06
		Mean	11.15	88.10	3.10	0.41	0.028	7.22	2.59	1.03	0.023	6.71	0.093	1.31	0.30
		Standard Deviation	1.14	3.36	1.70	0.105	0.022	1.82	0.95	0.167	0.013	4.1	0.144	1.36	0.249
20–30 minutes after infusion		Range	.....	96.2/83.6	7.1/5.3	0.64/0.35	0.111/0.03	8.5/3.79	3.4/0.9	1.23/0.84	0.042/0.0007	16.05/4.58	0.95/0.02	1.60/0.45	0.491/0.20
		Mean	.....	91.4	6.2	0.45	0.05	6.16	1.75	1.02	0.016	8.22	0.31	1.17	0.34
		Standard Deviation	.....	5.7	0.33	0.134	0.04	2.04	1.73	0.173	0.015	2.82	0.298	.608	0.13
Sum of Differences*		.....	.....	+13.1	+12.2	+.15	+.09	−4.23	3.37	−.06	−.104	+9.09	+1.28	−1.82	+.30
No. Observations		.....	.....	4	4	4	4	4	4	5	5	6	6	6	6
Mean		.....	.....	+3.3	+3.0	+.038	+.022	−1.06	−.84	−.012	−.021	+1.52	+.21	−.30	+.05
S.E.		.....	.....	.....	1.15	.....	.....	.....	.....	.....	.....	.....	0.18	.....	.....

TABLE III (*Continued*)

Patients	Diagnosis	Myocardial Usage (100/gm./min.)								Oxygen Extraction Ratio (%)						Oxygen Extraction Ratio	
		Coronary Flow	Oxygen (cc.)	Glucose (mg.)	Pyruvate (mg.)	Lactate (mg.)	Fatty Acids (mEq.)	Amino Acids (mg./N_2)	Ketones (mg.)	Glucose	Pyruvate	Lactate	Fatty Acids	Amino Acids	Ketones	Carbo-hydrates	Non-carbohydrates
1. A. E.	Essential hypertension	..	....	....	....	....	.....	....	....	12.2	0	11.1	207.0	3.5	5.2	23.3	215.7
		..	....	....	....	....	.....	....	....	23.2	1.57	9.2	132.0	19.8	6.7	33.9	158.5
		..	....	....	....	....	.....	....	....	36.3	0.64	6.1	33.0	13.3	4.5	43.0	50.8
2. J. A.	Essential hypertension	..	....	....	....	....	.....	....	....	.....	.....	.....	.....	0	0.66	.....	.....
		..	....	....	....	....	.....	....	....	.....	.....	.....	.....	32.5	0.89	.....	.....
		..	....	....	....	....	.....	....	....	.....	.....	.....	.....	8.6	3.6	.....	.....
3. M.C.L.	Essential hypertension	..	....	....	....	....	.....	....	....	.....	.....	.....	67.0	0.45	0.55	.....	68.0
		..	....	....	....	....	.....	....	....	.....	.....	.....	.....	.....	1.39	.....	.....
		..	....	....	....	....	.....	....	....	.....	.....	.....	201.0	0.90	4.16	.....	206.1
4. D. A.	Ca. of stomach	..	....	....	....	....	.....	....	....	28.5	1.92	24.0	31.0	2.7	2.5	54.4	36.2
		..	....	....	....	....	.....	....	....	38.0	0.25	22.6	.....	.....	2.17	60.8	.....
		..	....	....	....	....	.....	....	....	41.0	0.15	20.2	119.0	5.4	1.6	61.4	126.0
5. V. G.	Hyperthyroidism	..	....	....	....	....	.....	....	....	30.5	0.33	14.2	93.0	16.8	0.69	45.0	110.5
		..	....	....	....	....	.....	....	....	37.5	0.16	13.7	.....	.....	0.69	51.4	.....
		..	....	....	....	....	.....	....	....	46.0	0.22	9.2	0	39.8	1.8	55.4	41.6
6. E. L. H.	H.C.V.D.	90	10.7	0.90	0.03	2.28	0.03	0	0.62	6.8	0.18	15.8	130.0	0	5.9	22.8	136.0
		90	10.5	4.80	0.02	1.15	0.007	0.24	0.35	33.6	0.14	8.2	35.0	11.0	3.28	42.1	49.2
Control		..	....	....	....	....	.....	....	....	30.5/6.8	1.92/0	24.0/11.1	207/31	16.8/0	5.9/0.55	54.4/22.3	215/7.36/2
		..	....	....	....	....	.....	....	....	19.5	0.61	13.8	105.6	3.91	258	36.38	113.28
		..	....	....	....	....	.....	....	....	10.66	0.764	9.82	60.02	5.91	2.21	13.72	66.34
20–30 minutes after infusion		..	....	....	....	....	.....	....	....	46.0/36.3	0.64/0.15	20.2/6.1	201/0	39.8/0.9	4.5/1.6	61.9/43.0	206.9/41.6
		..	....	....	....	....	.....	....	....	39.2	0.28	10.9	77.6	13.7	3.16	50.72	94.74
		..	....	....	....	....	.....	....	....	4.93	0.22	5.52	73.2	12.53	1.1	6.53	63.57
Sum of Differences*		..	....	....	....	....	.....	....	....	+79.9	−1.28	−21.4	−.3160	+55.55	+4.44	+55.6	−92
No. Observations		..	....	....	....	....	.....	....	....	4	4	4	5	6	6	4	− 5
Mean		..	....	....	....	....	.....	....	....	+20.0	− .32	−5.4	−63.2	+9.28	+ .74	+13.9	−18.5
S.E.		..	....	....	....	....	.....	....	....	7.8	.....	.....	.....	.....	.....	.....	.....

* Obtained by taking difference between control and values observed 20 to 30 minutes after infusion. The number arrived at is the algebraic sum of these values.

likely that, in contrast to fatty acids which may be stored, the disappearance of ketone bodies from coronary blood is the result of complete oxidation for energy producing processes.[29a] Heart muscle appears to be unable to convert butyrate to carbohydrate via acetone.[29b] Consequently, the oxygen extraction ratio of ketones probably represents a true index of the percentage of oxygen used by the heart in the aerobic metabolism of these compounds. Barnes and co-workers using the heart-lung preparation found much higher values for the percentage of total myocardial oxygen consumed in the aerobic metabolism of beta-hydroxybutyric acid.[10] However, the initial concentration of this compound in the perfusate was at least ten times as high as that in the blood of the patients of this series.[10]

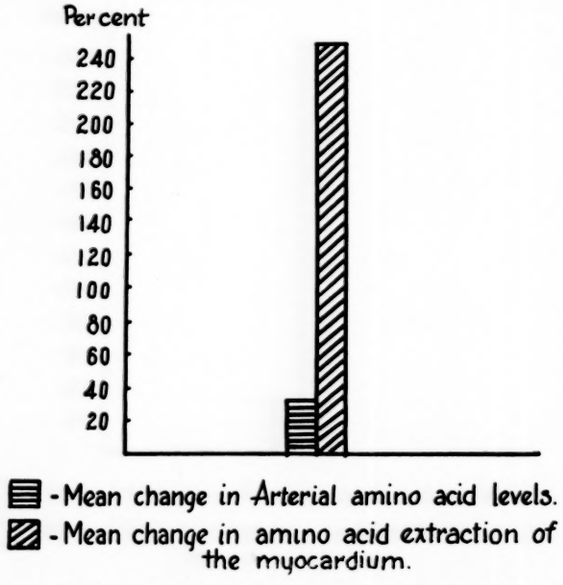


FIG. 2. The effect of the infusion of a protein hydrolysate on myocardial extraction of amino acids. A slight rise in blood amino acid concentration results in a disproportionate increase in their myocardial extraction.

Amino acids were extracted from the coronary blood, the extractions ranging from 0 to 0.45 mg. per cent of nitrogen, with an average of 0.132 mg. per cent and a standard deviation of 0.167. The myocardial oxygen extraction ratios of amino acids varied from 0 to 26 per cent, with an average of 5.6 per cent and a standard deviation of 6.9. Assuming aerobic breakdown, this implies that a considerable fraction of the oxygen consumption of the heart can be ascribed to the breakdown of amino acids. Van Slyke and Mayer also found that after injection of amino nitrogen into dogs the amino nitrogen content of skeletal muscle increased significantly until a saturation point was reached.[30a] These findings are in contrast to those of Cruickshank and McClure already referred to.

In order to test further the capacity of the human heart to utilize amino acids, protein hydrolysate (aminosol) was infused intravenously into six patients. It may be seen from Table III that the infusion resulted in an average rise in blood amino acid level of 1.52 mg. per cent nitrogen after twenty or thirty minutes of infusion. This was accompanied by an average increase in myocardial amino acid extraction of 0.21 mg. per cent of nitrogen. This rise was out of proportion to the small increase in the blood level of amino acids. Table III and Figure 2 illustrate that the average rise in blood amino acid level was 20 per cent, as compared to an average rise in myocardial amino acid extraction of 245 per cent. Simultaneously with the elevation in myocardial amino acid extraction there was a rise in extraction of glucose after twenty or thirty minutes, averaging 3.0 mg. per cent or 107 per cent; this is significant since it represents more than twice the standard error. (Table III.) There was no constant effect of the amino acid infusion on the extraction of other foodstuffs. The finding of increased extraction of amino acids from the blood with increased blood levels is consistent with the report of Van Slyke and Meyer who found that the concentration of amino acids in the muscle could be increased to three times its initial value.[30a] This phenomenon appeared to be an expedient for the conservation of amino acids.[30a] The finding of a positive nitrogen balance for the human heart points toward a rapid turnover of tissue proteins in heart muscle, in contrast to skeletal muscle where much of the protein mass may be metabolically almost inert.[31] It is likely that the results observed are but the over-all expression of transamination followed by oxidation, and that in heart muscle the amino acids must participate in the continuing activities of nonspecific tissue metabolism through exchange and transformation.[32]

COMMENTS

Results described in this paper demonstrate that the human heart muscle utilizes considerable quantities of non-carbohydrate substances such as fatty acids, ketone bodies and amino acids. (Tables I to III.) The myocardial extraction ratio of fatty acids is particularly great after

a high fat intake. (Table III.) In these patients the myocardial oxygen extraction ratio of fatty acids was frequently above 100 per cent and statistical analysis confirms the difference between patients in the postabsorptive state and after ingestion of fatty acids. (Fig. 1, Tables II and III.) Two possible explanations for these high ratios may be suggested. One is that the metabolism of fatty acids is increased, the second is storage of fat in the heart muscle. Skeletal muscle appears to be able to utilize fats, as demonstrated by Richardson, Shorr and Loebel.[25] Whether fats or proteins are used as fuel by the muscle seems to depend upon the relative amount of the two foodstuffs available and the ability of the enzyme systems to oxidize carbohydrates.[32] Thus in the starving subject, after the glycogen reserve in the liver has been exhausted, skeletal muscle derives most of its fuel from the metabolism of fat. The diabetic muscle also is forced to utilize fat;[25] under these conditions fatty acids may be broken down in the muscle into 2-carbon compounds that can be burned directly.[29a] It is likely that even with a slight fall in circulating carbohydrates most of the energy production is sustained by fat. It has been shown that after an overnight fast three-fifths of the energy production is sustained by fats. Apparently when there is no continuous exogenous supply of carbohydrate the endogenous supply is used with increasing economy.[29a] It is likely from work reported in this paper, as well as from experiments on the isolated heart, that the myocardium, like skeletal muscle, can use fats as fuel for energy production.

Storage of fat by the heart is suggested by the data represented in Table II. In five of seven patients ingestion of fat resulted in oxygen extraction ratios over 100 per cent. (Fig. 1.) Furthermore, the average ratio between non-carbohydrate and carbohydrate oxygen extraction ratio was 4.6/1 whereas in the postabsorptive state this ratio was only 2.0/1. Since only fatty acids were responsible for the increase in this ratio following their ingestion, storage of these substances by the heart is the best possibility. Kohl found that fat is stored if the fat intake exceeds the demands of the tissues to supply metabolic needs.[33] Since capacity to store glycogen in heart muscle is probably limited, the myocardium is forced to utilize fat. Evidence for the storage of fat in heart muscle has been obtained by Wegelin who produced alimentary lipemia and demonstrated fat infiltration into the interfibrillar sarcoplasm and the cross sectional parallel fibers of heart muscle.[26] Similar results were obtained by the present authors in the hearts of dogs sacrificed three hours after oral administration of 3 ounces of lipomul.[27]

The results summarized in Tables I to III show that the human heart utilizes ketones, thus confirming the finding of Barnes and of Waters and their associates.[10,11] The aerobic metabolism of ketone bodies accounts for from 0.55 to 10.4 per cent of the total oxygen extraction of the heart, with a mean of 4.38 and a standard deviation of 3.1. This figure is considerably less than that of Barnes and of Waters who found that as much as 80 per cent of the total oxygen consumption of the heart lung may be ascribed to beta hydroxybutyrate; however, the concentration of ketones in the arterial blood of the patients studied was much lower than in the perfusates used by these workers.[10,11]

The metabolic pathway of ketones in heart muscle is not clear from these results. It is possible, however, that under certain conditions such as diabetes or starvation ketones take over some of the energy-producing functions in the muscle through formation of oxalacetic acid.[29a] It is unlikely that there is net conversion of fat via acetone to carbohydrates in heart muscle since Lorber, in studying the metabolism of beta-C^{14}-butyrate, found that isotope was incorporated only into the carboxyl groups of lactate and pyruvate.[29b] Figure 3 illustrates a negative correlation between carbohydrate and ketone utilization with a coefficient of correlation of -6.32 with a standard error of 2.76, which is statistically highly significant. Apparently carbohydrates inhibit ketone utilization by the heart, a finding which is in accord with Krebs' demonstration in the Warburg apparatus that deamination of amino acids is inhibited by oxidizable substrates.[34] Edson later showed a similar competition in the liver between fatty acids and other oxidizable substrates.[35] Waters et al. demonstrated in the heart-lung preparation that when both carbohydrate and ketone bodies are available, the former is used preferentially.[11]

Amino acids are extracted in considerable quantity from the coronary blood (Tables I to III), a finding which contrasts with that of Cruickshank in the heart-lung preparation.[12] After infusion of amino acids as much as 40 per cent of the total cardiac oxygen consumption can be accounted for by aerobic metabolism of amino acids (V. G., Table III.) A small rise in

arterial amino acid concentration produced a disproportionate increase in their myocardial extraction. (Fig. 2.) Thus the average rise in blood amino acid level was 20 per cent, as compared with an average rise in myocardial amino acid extraction of 245 per cent. It has

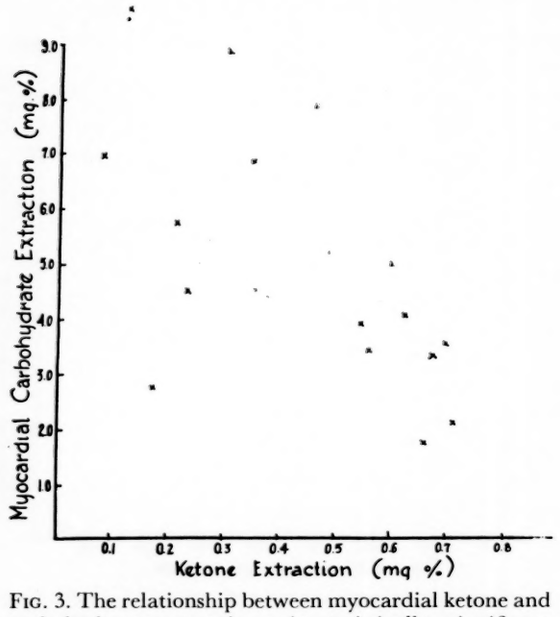


FIG. 3. The relationship between myocardial ketone and carbohydrate extraction. A statistically significant negative correlation exists, indicating that carbohydrates inhibit ketone utilization by the heart.

been shown that tissues take up amino acids rapidly when their concentration in blood is increased.[30a] This does not mean that they are stored like fatty acids or glycogen. It is also unlikely that amino groups of blood and tissue are directly involved in the chemical processes of muscular contraction. However, there are other ways to explain the uptake of amino groups by the heart. Amino acids may be converted into carbohydrates; the majority can form glycogen, which may be stored in the heart to be used later for the provision of energy. Another likely possibility is that amino acids are subjected to metabolic exchange and transformation. According to Schoenheimer, amino acids are continuously transformed into other nitrogenous compounds and find their way not only into other amino acids but are incorporated into proteins and appear among the end-products of protein metabolism.[36] It is likely on the basis of this work that there is a continuous exchange between exogenous and endogenous amino acids, both of which can be taken up by tissue proteins. The possibility exists on the basis of recent work that this is accomplished by transamination followed by oxidation.[30a]

Statistical analysis of the data represented in Tables I to III reveals a large scatter of almost all observations. This is illustrated by the large coefficients of variations. (Tables I to III.) There may be several explanations for the large scatter. In the first place, the data are collected from a non-uniform population. The patients had various cardiac disorders, their age and body build were different. Secondly, errors in analytical procedures may have contributed to the scatter; however, none of the methods used have an analytical error of more than 5 per cent and in most of them the error is less than 2 per cent. Finally, a large statistical error may result from the small sample size. Although all these factors contribute to the large scatter, it is more likely that the high coefficient of variation results chiefly from physiologic variations, that is, the variability of the factors. Each heart appears to be geared to its own metabolic needs and requirements. These, in turn, depend on the general metabolic state of the body, as expressed in the composition of the blood perfusing the heart, and on the metabolic requirements of the heart muscle itself.

SUMMARY

The myocardial extraction of fatty acids, ketone bodies and amino acids was measured in thirty-three patients. The heart extracted considerable amounts of these non-carbohydrate foodstuffs. Myocardial extraction ratios of fatty acids were particularly great after a high fat intake, suggesting storage of fat in the heart muscle.

A negative correlation between myocardial carbohydrate and ketone utilization was observed; this finding is in accord with the theory of substrate competition for available oxygen.

During infusion of amino acids the rise in arterial amino acid concentration produced a disproportionate increase in their myocardial extraction and a considerable increase in glucose extraction by the heart.

Statistical analysis of the data revealed a large scatter in almost all observations. It seems likely that this was the outcome of physiologic variations resulting from differences in the metabolic needs and requirements of the heart.

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Effect of Banthine on the Cardiac Mechanism in States Associated with Increased Vagal Tone*

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BANTHINE® is a quaternary ammonium compound, β-diethyl amino-ethyl xanthene-9-carboxylate metho-bromide, that has recently been demonstrated to have a powerful anticholinergic action.[1–7] In low concentration it produces an atropine-like effect in blocking post-ganglionic parasympathetic endings; larger doses block autonomic ganglia as well. It has been widely used experimentally and clinically in reducing gastric motility and secretion. Its cholinergic blocking effect is comparable to that of atropine. Recent reports[8] indicate that banthine is superior to atropine in relieving smooth muscle spasm in the gastrointestinal tract. Recently Evans[9] controlled the symptoms of six of ten patients with the carotid sinus syndrome with oral banthine (50 to 100 mg., three to four times daily) and Labecki[10] has reported a case of heart block treated with banthine. It has been used preoperatively in patients with increased vagal tone in order to reduce the incidence of arrhythmias.[11] The purpose of this study was to determine the antivagal effect of banthine in cardiovascular states accompanied by increased vagal tone, i.e., partial A-V heart block and the cardioinhibitory type of carotid sinus syndrome.

METHODS OF STUDY

The patients included in the study comprised two main categories: (1) those who showed electrocardiographic evidence of first or second degree or complete A-V heart block and (2) patients with the cardioinhibitory type of carotid sinus syncope. The last group exhibited a hypersensitive carotid sinus mechanism with resultant production of cardiac standstill following carotid sinus pressure. The effect of banthine was studied in twelve patients (ten male and two female) whose ages ranged from ten to eighty years. The cases were classified as follows: hypersensitive carotid sinus syndrome, six cases; A-V heart block, six cases, two of which were first degree heart block, two were second degree, and two had complete A-V heart block. In addition, the effect of this drug was studied in a subject with coronary sinus rhythm and one with Wolff-Parkinson-White syndrome.

An intravenous injection of banthine, 5 to 10 mg., was given. In all but one patient in this group the administration was rapid, within about one minute. The electrocardiographic effects were determined by continuous recording for five to ten minutes after injection in all cases, and frequent observations for one hour thereafter. In addition, banthine (100 to 400 mg.) was administered via the oral route in eight of the subjects after the intravenous response was determined. Probanthine,® 15 mg. orally, twice or three times daily, was given for a period of one month to two patients with carotid sinus syncope. The effects on carotid sinus sensitivity and any untoward symptoms were noted during the period of its clinical activity.

RESULTS

Intravenous Route. Following the intravenous administration of banthine, 5 mg. in five cases and 10 mg. in six cases, the ventricular rate increased from 20 to 80 beats per minute above the control value. Prolonged P-R intervals were shortened from 0.40 to 0.60 second below the premedication values. The maximum increase in ventricular rate and shortening of the P-R interval was observed within forty-five to ninety

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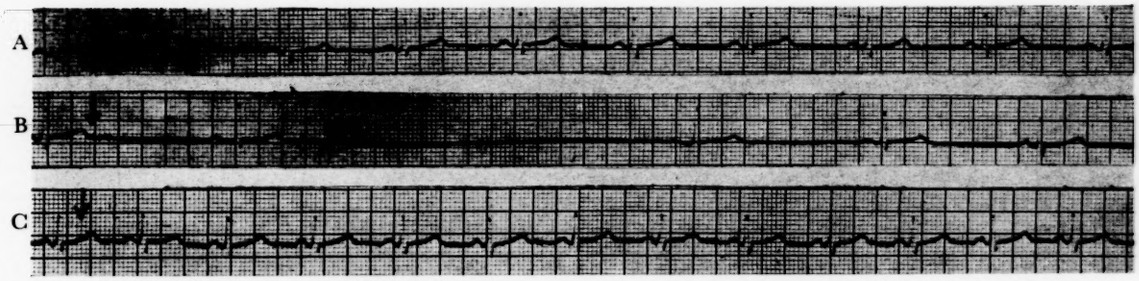


FIG. 1. A, control tracing (lead II) shows normal sinus rhythm, rate 60 per minute; B, right carotid sinus pressure applied at arrow. Note period of cardiac standstill (four seconds); C, ninety seconds after 5 mg. of banthine intravenously. The rate has increased from 60 in the control to 78 per minute. Carotid sinus pressure applied at arrow failed to produce any slowing.

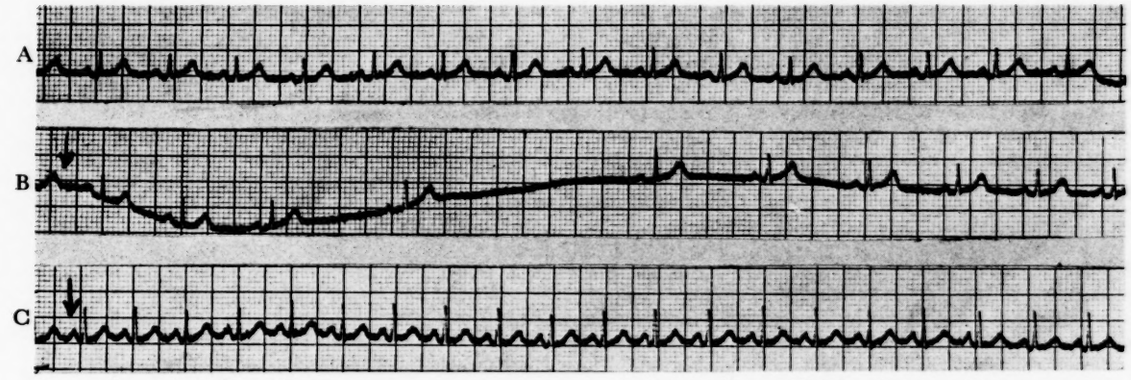


FIG. 2. A, control (lead II). Note regular rhythm at a rate of 107 per minute; B, following carotid sinus pressure at arrow, note marked slowing of rate; C, rate = 150 per minute; ninety seconds after 5 mg. of banthine intravenously. Carotid sinus pressure no longer results in slowing.

seconds following intravenous administration. The hypersensitive carotid sinus reflex was abolished in all of the six cases of our series. The carotid sinus sensitivity disappeared when the tachycardia was first noted (forty-five to ninety seconds after injection; see Figs. 1, 2 and 3) and no cardioinhibitory effect could be elicited subsequently by carotid sinus pressure for a mean period from four to six hours; in one instance the reflex was abolished for twelve hours following the intravenous administration of 10 mg. of banthine. No electrocardiographic effect was observed in the case of coronary sinus rhythm; in the two cases of complete A-V heart block the auricular rate was increased whereas the ventricular rate was unchanged. (Fig. 4.) In the one case of Wolff-Parkinson-White syndrome the QRS complex was shortened from 0.12 to 0.10 second whereas the P-R interval was apparently unchanged. (Fig. 4C.)

Oral Administration. Banthine was given orally to the six patients with the cardioinhibitory type of carotid sinus syndrome and to one patient with partial A-V heart block, a ten year old male who was subject to fainting spells. The cardio-accelerator effect occurred within fifteen minutes to one and one-half hours after the oral administration of 50 mg. of banthine in five of the six patients, and lasted three to six hours. In two patients followed for a period of four weeks the syncopal episodes disappeared and no cardioinhibitory response to carotid sinus pressure could be elicited on a regimen of 100 mg. of banthine a day. When 200 mg. of banthine were given per day, in divided doses, the cardioinhibitory response to carotid sinus pressure was abolished in four additional cases. One patient with a hypersensitive carotid sinus and associated Ménière's disease with right labyrinthitis continued to experience symptoms of dizziness and weakness and the cardioinhibitory effect of carotid sinus pressure persisted despite the administration of 400 mg. of banthine per day.

Side Effects. Dryness of the mouth, dilatation of the pupils, weakness of the detrusor muscle with urinary retention were the side effects noted in six cases in the present series; these effects usually disappeared within one to two hours after oral administration. No untoward or toxic effects were noted with banthine, but following

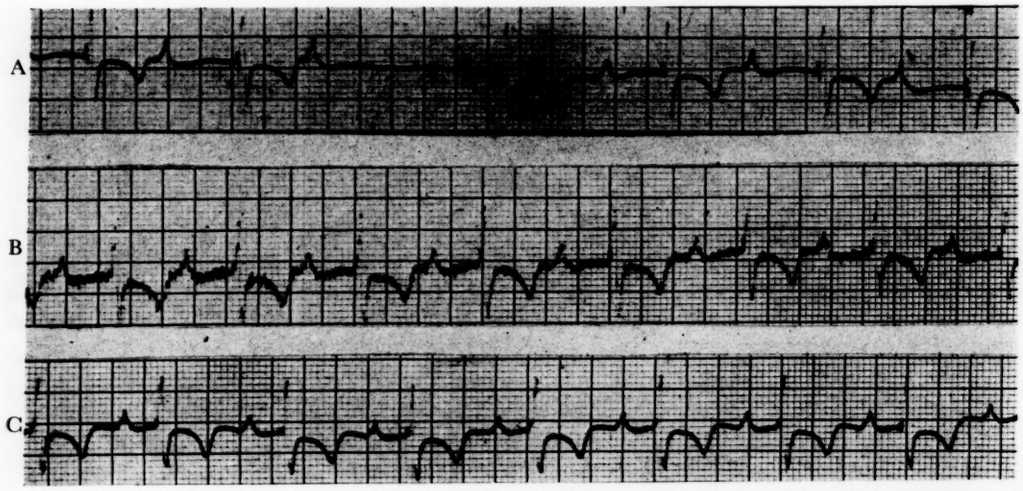


FIG. 3. A, control (lead V_2) shows prolonged P-R interval measuring 0.44 second with dropped beats; B, after needle is put in vein before banthine the P-R interval is 0.36 second; C, two minutes after banthine was administered intravenously, the auricular and ventricular rates have increased to 88 per minute and the P-R interval now measures 0.24 second.

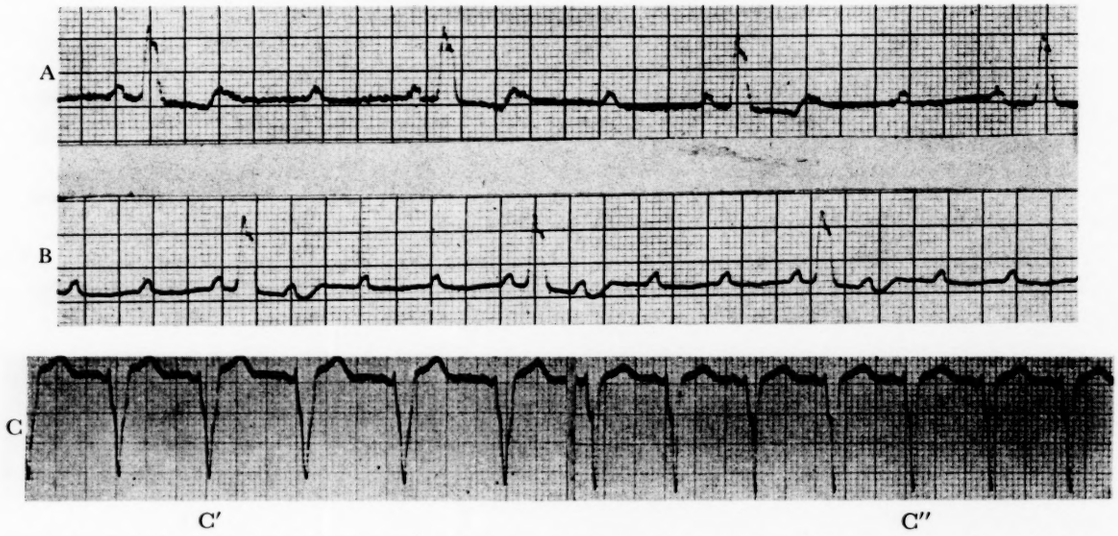


FIG. 4. A, control. Complete A-V heart block is present. The auricular rate is 100 per minute, the ventricular rate is 36 per minute; B, one minute after 10 mg. of banthine was administered intravenously there is no change in the ventricular rate; the auricular rate, however, is increased to 140 per minute. C, this patient showed the typical electrocardiographic pattern of a W-P-W syndrome. Only V_1 is shown in this figure; C′, control (lead V_1) before banthine shows notched widened QRS complexes. The notching is particularly marked in the downstroke of the QRS complex. The P-R interval measures 0.08 second and the ventricular rate is slightly irregular and measures 88 per minute. The QRS complex measures 0.12 second; C″, one minute after 3 mg. of banthine intravenously; note the increase in the ventricular rate to 115 per minute and shortening of the QRS complex to 0.10 second without any significant change in the P-R interval.

the oral administration of probanthine in two patients one developed an erythema multiforme type of skin eruption.

COMMENTS

It appears from this study that, in accordance with the work of previous investigators,[1–11] banthine in the dosage employed exerts a powerful atropine-like effect on the cardiovascular system. The vagolytic effects of the drug included tachycardia and consequent shortening of the P-R interval. By the intravenous route the effects were evident within one to two minutes and lasted two to six hours. By the oral

route the effects were evident within one-half to one and one-half hours but the tachycardia was slight and the P-R interval was unchanged. The hyperactive carotid sinus reflex was abolished by both routes, the maximum response apparently corresponding with the onset of tachycardia.

Banthine appears to be a useful adjunct in the treatment of cardiovascular conditions characterized by increased vagal tone. Thus, hypersensitive carotid sinus syndrome and various degrees of heart block can be abolished by the atropine-like effects of banthine. However, in the two cases of complete A-V heart block studied the auricular rate was accelerated but the ventricular rate was unchanged. The side effects consisted of dryness of the mouth, blurring of vision and, in one instance, urinary retention; the last was promptly relieved by prostigmine. Extreme drowsiness was noted with large doses of probanthine. A skin eruption of the erythema multiforme type occurred four days following the administration of probanthine, 45 mg. per day, in one of the two patients studied with this drug.

There is some difference of opinion concerning the relative potency of the anticholinergic effects of banthine as compared with those of atropine. In one report[12] the anticholinergic neuroeffector blocking action of banthine, as measured by its anticholinergic spasmolytic activity on the excised rabbit ileum and also by the antimecholyl chromodacryorrhea test, was 0.7 that of atropine. On the other hand, Benjamin et al.,[6] in comparing the effectiveness of banthine and atropine in depressing gastric acid secretion both in man and in the dog found that 1.2 mg. of atropine was comparable to 10 mg. of banthine in effect. Even assuming an atropine/banthine ratio of 1.2:10, as observed by Benjamin, satisfactory vagolytic effects of banthine would seem to be accompanied by considerably less side effects than with a comparable dose of atropine. If one assumes that banthine has 0.7 the potency of atropine in its anticholinergic effect, considerably more banthine than atropine can be given in treating the effects of increased vagal tone without concomitant untoward effects. For example, 2.4 mg. ($\frac{1}{25}$ gr.) of atropine intravenously is usually followed by marked side effects whereas a comparable dose of banthine is accompanied by little or no side reaction. Doses of 5 to 10 mg. of banthine used in this study were accompanied by no significant untoward effects. Like atropine, the efficacy of banthine is limited to abolition of excess vagal tone and seems to have no particular pharmacologic action not observed with atropine.

SUMMARY

1. Banthine (5 to 10 mg.) was given intravenously to eleven patients and administered orally (100 to 400 mg. daily) to eight patients. These included subjects with A-V heart block (six cases), hypersensitive carotid sinus syndrome (six cases), Wolff-Parkinson-White syndrome and coronary sinus rhythm (one case each).

2. Banthine appears to be an efficacious agent in combatting excessive vagal tone involving the cardiovascular system.

3. Following the intravenous administration of banthine, tachycardia and shortening of the P-R interval occurred within forty-five to ninety seconds, these effects persisting for four to six hours.

4. Banthine administered orally produced a moderate tachycardia within thirty minutes to one and one-half hours. This persisted for three to six hours.

5. The carotid sinus reflex was abolished in all six cases when the oral route was used.

6. Relatively large, therapeutically effective doses of banthine can be administered with fewer side effects than are observed with comparable doses of atropine.

Acknowledgment: The banthine and probanthine used in this study were furnished by the G. D. Searle and Company.

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Pulmonary Stenosis with Left to Right Intracardiac Shunts*

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THE combination of pulmonary stenosis with atrial or ventricular septal defects is usually associated with decreased blood flow to the lungs and intracardiac shunting of blood from right to left resulting in cyanosis. Non-cyanotic patients with clinical evidence of pulmonic stenosis have generally been considered to have isolated pulmonic stenosis with intact septa. The purpose of this paper is to report a group of patients with pulmonary stenosis who, in spite of having associated septal defects, had no definite cyanosis at rest and had predominant left to right intracardiac shunts.

CASE REPORTS

CASE I. C. K., a twelve year old female, was known to have had a heart murmur since the age of four months. At the age of four years during an attack of pertussis, cyanosis was observed temporarily. Since that time the only symptom has been a poor appetite. There have been no further episodes of cyanosis.

The physical examination disclosed an intelligent girl who was slender and physically underdeveloped. Her height was 54½ inches and weight 50½ pounds. The blood pressure was 105/60 in the arms and 150/80 in the legs. Her pulse was 90. No cyanosis or clubbing was present. The heart was slightly enlarged to percussion. A harsh rough systolic murmur accompanied by a thrill was heard over the precordium, loudest in the third left intercostal space. The rhythm was regular. The second sound in the pulmonic area was diminished in intensity.

The hemoglobin was 12.3 gm., red blood cells 4.1 million. An electrocardiogram showed right ventricular hypertrophy. Fluoroscopy showed an enlarged cardiac shadow due primarily to right ventricular hypertrophy. The hilar vessels were prominent and the lung fields appeared normal. Cardiac catheterization data presented in Table I indicated a diagnosis of infundibular stenosis and ventricular septal defect.

CASE II. M. A. H., a twenty-two year old woman, was known to have a heart murmur since childhood but had no limitation of physical activity. At the age of eighteen she gave birth to a daughter following an uneventful pregnancy and labor. One year later she noted the onset of weakness, tiredness and dyspnea. She was hospitalized elsewhere and digitalized. Subsequently her activities were restricted by exertional dyspnea and palpitation. There was no history of cyanosis.

On physical examination the patient did not appear acutely ill. Her pulse was 86, respirations 20 and blood pressure 120/80. There was no cyanosis or clubbing. Cardiovascular examination revealed moderate cardiac enlargement with regular rhythm. A systolic murmur with a thrill was present in the pulmonic area and the murmur was widely transmitted throughout the precordium. The liver edge was palpable at the right costal margin. The femoral arterial pulsations were normal. There was no dependent edema. The remainder of the examination was not remarkable.

The hemoglobin determination was 11.7 gm. An electrocardiogram showed incomplete right bundle branch block and digitalis effect. On cardiac fluoroscopy moderate right ventricular hypertrophy was noted. The hilar vessels were prominent but no pulsations could be seen. The lung fields appeared normal. An angiocardiogram showed narrowing of the right

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ventricular outflow tract. Cardiac catheterization revealed a higher oxygen saturation in the pulmonary artery than in the right ventricle, and two sites of pressure change believed to represent valvular and infundibular stenosis. Because of the patient's normal pulse pressure and the absence of a continuous murmur, the left to right shunt of oxygenated blood was thought to be due to a ventricular septal defect rather than to an aortic-pulmonary communication.

Because of the low pulmonary artery pressure, valvulotomy was performed. Pressure measurements obtained at operation disclosed systolic pressures of 10 mm. Hg in the pulmonary artery, 50 mm. in the outflow tract of the right ventricle, and 70 mm. low in the right ventricle. During digital exploration of the right ventricle the infundibulum seemed adequate but the pulmonary valve appeared to be narrowed and was possibly torn by the exploring finger. A dilator, set at 24 mm. diameter, was introduced into the right ventricle and passed into the pulmonary artery with ease. Nevertheless, pressure measurements immediately following this procedure were unchanged. During the operation and for a short time thereafter the patient was moderately hypotensive. Her subsequent postoperative course was uneventful. Follow-up examination six months postoperatively revealed little clinical improvement.

Case III. L. A., a twelve year old boy, was known to have had a heart murmur since the age of four months. He was well until the age of nine years when progressive fatiguability, occasional cyanosis of the lips and nailbeds and dyspnea appeared. He squatted frequently in order to get his breath. By the time of admission to the Hospital of the University of Pennsylvania his exercise tolerance was grossly impaired. While climbing stairs he had to cling to the railing every two or three steps in order to rest. He was exhausted by a two-block walk from his home to school.

Physical examination revealed an apparently normally developed child. His height was 58 inches and weight 88½ pounds. His pulse was 88, respirations 24 and blood pressure 90/70. At times a slight purplish hue was noted in his lips and nailbeds. Beginning clubbing of the digits was observed. A slight kyphoscoliosis was present. The heart was not enlarged by percussion and the rhythm was regular. A systolic thrill was palpable from the clavicle to the third intercostal space along the left sternal border. A harsh systolic murmur loudest in the second and third left intercostal spaces was widely transmitted throughout the precordium and to the left side of the neck. The liver edge was not palpable and there was no edema.

The hemoglobin was 15.6 gm., red blood cells, 5.6 million. An electrocardiogram showed right ventricular hypertrophy. Chest x-ray and fluoroscopy showed right ventricular enlargement with upward displacement of the cardiac apex and some degree of concavity of the left upper cardiac border simulating the "coeur-en-sabot" appearance. The transverse and descending portions of the aorta were on the right. The lung fields were unusually clear. Angiocardiograms showed no early opacification of the aorta but were inconclusive regarding the presence of pulmonic stenosis.

Skin oxygen tension by the polarographic method[1] revealed an increase in oxygen tension of 214 per cent following inhalation of 100 per cent oxygen. This is within the normal range of increase which occurs in individuals without right to left shunts. In patients with proven right to left shunts the maximum observed has not exceeded 100 per cent.[1] After sixteen step-ups 12 inches high, there was a significant decrease of 15 per cent in oxygen saturation as measured by the oximeter. These results were intrepreted as evidence that there was no significant right to left shunt at rest but that a significant shunt from right to left appeared after exercise. Cardiac catheterization data are presented in Table I. The diagnosis of valvular and infundibular pulmonic stenosis, ventricular septal defect and right aortic arch was made.

At operation a dilator was introduced into the pulmonary artery via the right ventricle and opened to 15 mm. diameter. No obstruction was encountered at the valve as the dilator was withdrawn but an obstruction was met in the infundibulum. Some muscle was removed from this area by means of a Brock punch. However, pressures in the pulmonary artery and right ventricle remained unchanged following this procedure and were essentially the same as those obtained at catheterization. The patient's postoperative course was difficult for several days because of retained bronchial secretions but thereafter was uneventful. Examination six months postoperatively revealed little if any clinical improvement.

Case IV. T. B., an eighteen year old white

female, was known to have had a heart murmur since birth. She suffered repeated respiratory infections in childhood and her physical development was delayed. The menarche occurred at the age of seventeen. She gave a history of diminished exercise tolerance with exertional dyspnea and slight cyanosis on exertion.

On physical examination her pulse was 80, respirations 16 and blood pressure 100/70. Blood pressure in the left leg was 120/70. No cyanosis, clubbing or edema was noted. Mild kyphosis of the thoracic spine was present. On examination of the heart the apex impulse was palpated in the sixth intercostal space in the left anterior axillary line. A systolic thrill was palpated and was of maximum intensity in the second left intercostal space. The rhythm was regular. A grade 4, harsh systolic murmur was heard maximally in the second left intercostal space and was transmitted throughout the precordium. The second sound in the pulmonic area was thought to be normal or slightly increased in intensity. The remainder of the physical examination revealed nothing abnormal.

Laboratory findings included a normal complete blood count and urinalysis. The electrocardiogram was within normal limits except that T-1 was of low amplitude. On cardiac fluoroscopy the heart was vertically placed, with enlargement of both ventricles. The pulmonary artery segment was prominent and pulsated vigorously. The upper mediastinal shadow was widened. The vascular markings in the lung fields were increased but no "hilar dance" was observed. The data obtained by cardiac catheterization are presented in Table I. In addition, the catheter entered an anomalous left superior vena cava. The final diagnosis was infundibular stenosis, ventricular septal defect and persistent left superior vena cava.

CASE V. R. B. was an eight year old boy in whom a cardiac murmur had been observed since infancy. He was asymptomatic. There was no history of cyanosis and his exercise tolerance was good.

The physical examination revealed a well developed child. His height was 48½ inches and weight was 47 pounds. The blood pressure was 80/40 in the arms and 90/50 in the left leg. There was no cyanosis or clubbing. A convergent strabismus was present. The cardiac rhythm was regular. A systolic thrill was present in the third left intercostal space. A loud systolic murmur was heard in this area transmitted to the left clavicle. The second sound in the pulmonic area was readily heard. The remainder of the examination revealed nothing abnormal.

The hemoglobin was 14.2 gm., red blood count, 4.7 million. Fluoroscopic examination of the heart revealed negative findings. An electrocardiogram revealed evidence of right ventricular hypertrophy with P wave contours suggesting auricular abnormality. The cardiac catheterization data are presented in Table I. A diagnosis of valvular pulmonic stenosis with atrial septal defect was made.

CASE VI. B. H. was a thirteen year old girl reported to have had a congenital heart lesion since infancy. She was asymptomatic and her exercise tolerance was good. There was no history of cyanosis. One younger brother was also said to have a congenital cardiac lesion.

Pertinent physical findings included a pulse rate of 90, blood pressure 116/60. She was well developed physically. The heart was not enlarged to percussion. A systolic thrill was palpated in the second and third left intercostal spaces. A systolic murmur was heard to be loudest in the same area but was widely transmitted throughout the precordium.

The hemoglobin was 12.2 gm. An electrocardiogram showed changes suggestive of right ventricular hypertrophy. Chest x-rays and cardiac fluoroscopy revealed a heart normal in size or slightly enlarged, with a prominent pulmonary artery segment and large pulsatile vessels at the hilus. The lung fields appeared well vascularized. The cardiac catheterization studies are summarized in Table I. A diagnosis of pulmonary valvular stenosis and atrial septal defect was made.

RESULTS

As the data in Table I indicate, in Cases I to IV pulmonic stenosis appeared to be associated with a ventricular septal defect. In Cases I, III and IV a shunt of oxygenated blood entering the right ventricle was demonstrated by the elevation of blood oxygen saturation in this chamber as compared to that of the right atrium. In Case III ventricular irritability precluded sampling from the right ventricle during cardiac catheterization but blood samples were obtained at operation ten days later. In Case II the exact site of the shunt was not definitely established since a blood sample was not obtained from the right ventricular outflow tract. Although the oxygen levels in this patient

were compatible with either an aortic-pulmonary arterial communication or a high ventricular septal defect, the normal pulse pressure and the absence of a continuous murmur made the latter diagnosis more likely.

In these first four patients continuous pressure recordings obtained during withdrawal of the catheter from the pulmonary artery through the right ventricle revealed one or two increases in pressure. In Cases I and IV a single pressure change occurred within the body of the right ventricle, interpreted as evidence of infundibular stenosis. (Fig. 1.) In Cases II and III two sites of pressure change were observed. The upper record in Figure 2 illustrates the pressures obtained in Case II. The first rise in pressure occurred as the catheter was withdrawn into the right ventricle from the pulmonary artery indicating pulmonary valvular stenosis. A second rise in pressure suggestive of infundibular stenosis was seen as the catheter was withdrawn through the outflow tract of the right ventricle.

In Cases V and VI the pulmonic stenosis was associated with a defect of the atrial septum. In both patients the oxygen saturations demonstrated a shunt of oxygenated blood entering the right atrium, and the catheter was passed through the septal defect. The pressure recordings suggested the presence of valvular pulmonic stenosis without infundibular stenosis. (Lower record, Fig. 2.) In these two patients the right ventricular pressure, although elevated, was considerably lower than in those patients with evidence of ventricular septal defects.

TABLE I

CARDIAC CATHETERIZATION DATA*

Case No. and Name	Age	Hgb.‖ (gm.)	Pressure (mm. Hg)						Oxygen Saturation (%)							
			PA	RV out	RA in	RA	LA	LV	PA	RV out	RV in	RA	SVC	PV	LA	FA
I—C. K.	12	13.3	53/23	50/4	100/5	5/1	...	...	85.6	85.7	81.7	73.0	71.8	....	....	95.2
II—M. A. H.	21	12.3	20/10	62/3	102/7	10/2	...	...	83.6†	.....	77.0	74.6 67.6	70.0	....	....	95.7
III—L. A.	12	15.6	10/0	40/4	90/4	3/−3	...	...	76.9	83.1‡	....	69.9 77.6‡	71.3	....	....	....
IV—T. B.	19	11.8	41/11	45/3	93/7	6/2	...	...	87.9	86.6	84.6	66.4	68.2 72.2§	....	....	95.7
V—R. B.	8	12.8	14/4	43/0	43/0	2/0	2/−1	...	86.1	.....	88.5	82.8	78.5	98.8	96.2	....
VI—B. H.	13	13.5	15/4	40/6	43/6	4/0	...	104/6	82.2	.....	83.7	85.8	73.8	....	95.1	96.0

* Pressure records were obtained by a Lilly capacitance manometer; oxygen determinations were done by the Van Slyke technic.[2]

† Sample from right pulmonary artery.

‡ Samples taken at operation ten days following cardiac catheterization.

§ Sample taken from persistent left superior vena cava.

‖ Determined at the time of cardiac catheterization.

Key: PA: Pulmonary artery
RV in: Inflow tract of the right ventricle
RV out: Outflow tract of the right ventricle
RA: Right atrium
LA: Left atrium
PV: Pulmonary vein
SVC: Superior vena cava
FA: Femoral artery

COMMENT

The combination of pulmonic stenosis with atrial or ventricular septal defects usually causes cyanosis by producing a right to left intracardiac shunt. However, in previous studies[3–5] cardiac catheterization has demonstrated that this combination of defects may at times permit left to right intracardiac shunts. In many of these reported cases pulmonary blood flow was not decreased and the patients were not cyanotic at rest. Whether a given patient with pulmonic

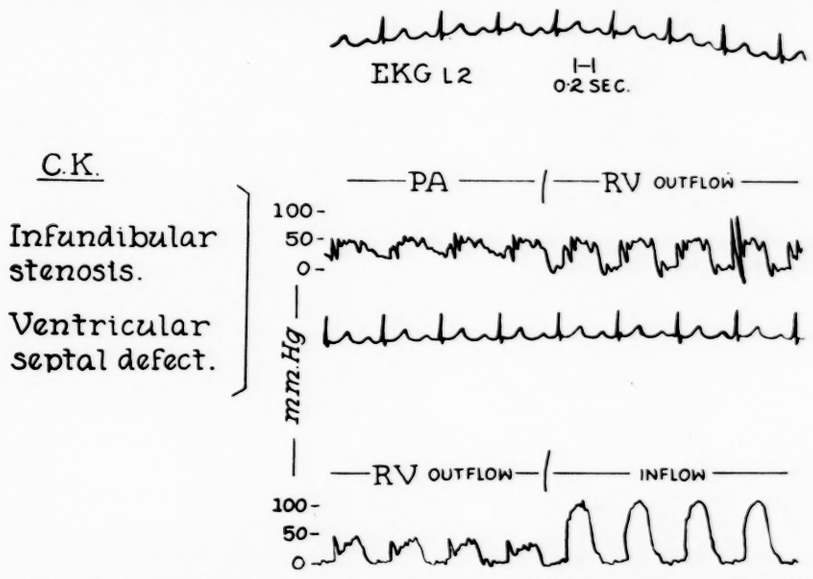


FIG. 1. Case I (C. K.). Upper record: simultaneous electrocardiogram (lead 2) and continuous pressure record obtained as the cardiac catheter was withdrawn from the pulmonary artery to the outflow tract of the right ventricle. Note the drop in the diastolic pressure with no change in the systolic pressure, as the catheter was withdrawn through the pulmonic valve. Lower record: the catheter was withdrawn from the outflow tract to the lower portion of the right ventricle. The abrupt rise in systolic pressure occurred at the site of the infundibular stenosis The pressure tracing has been retouched for clarity in reproduction.

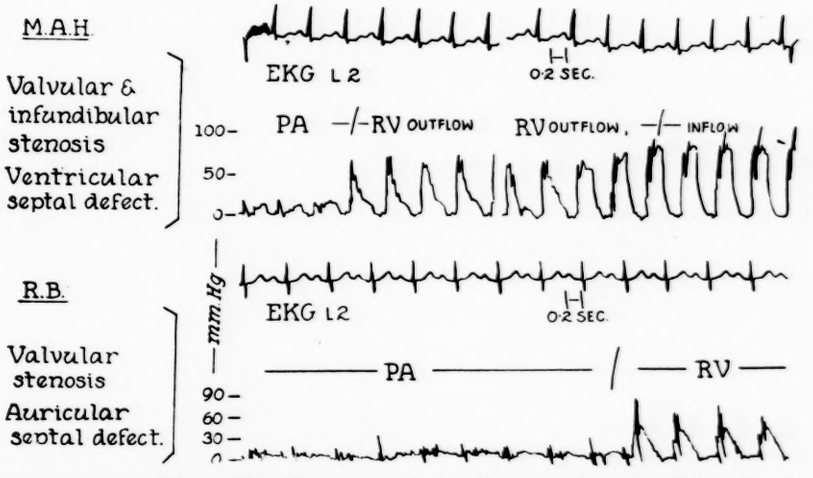


FIG. 2. Case II (M. A. H.). Upper record: simultaneous electrocardiogram and pressure record obtained as the catheter was withdrawn from the pulmonary artery to the region of the tricuspid valve. Note two rises in systolic pressure; one at the pulmonic valve and one in the outflow tract of the right ventricle. Lower record: Case V (R. B.). The catheter was withdrawn from the pulmonary artery to the right ventricle. Note the rise in systolic pressure at the pulmonic valve. There was no further change in pressure as the catheter was withdrawn through the right ventricle. The pressure tracings have been retouched for clarity in reproduction.

stenosis and a septal defect will be cyanotic or not must depend on the pressure relationships between the right and left sides of the heart. In those patients with atrial septal defects the major factors in determining the direction of the shunt probably are the degree of pulmonic stenosis and the compensation of the right ventricle. In those with ventricular septal defects the degree of overriding of the aorta, when present, is an additional factor of importance.

In the two patients (Cases V and VI) with pulmonic stenosis and atrial septal defects the right ventricular pressures suggested that the stenosis was not severe and that the right ventricle was well compensated. Interestingly, both these patients had pressure records compatible with valvular stenosis. This type of stenosis is found at necropsy in the majority of patients with pulmonary stenosis and intact ventricular septa.[6]

In the four patients (Cases I, II, III and IV) with pulmonic stenosis and ventricular septal defects it is interesting to speculate on the possibility of a relationship to the tetralogy of Fallot. First, all four patients had evidence of infundibular stenosis, which is the type usually found in the tetralogy of Fallot. Although two of these patients also had valvular stenosis. Brock and Campbell have recently pointed out that this combination may occur in patients with the tetralogy of Fallot.[7] Second, anatomic studies[8,9] have demonstrated that varying degrees of aortic dextroposition can occur, ranging from ventricular septal defects with inappreciable overriding to major degrees of aortic dextroposition. Furthermore, these studies have emphasized the difficulty of determining from the anatomic appearance of the specimen whether or not a mild degree of aortic dextroposition is present when there is a large defect of the membranous septum.

The difficulty of the clinical classification of some of these patients is illustrated by our third patient (L. A.). At rest, angiocardiography and polarographic oxygen determinations failed to indicate any right to left shunt. However, on exertion unsaturation occurred, as shown by oximetry. These studies demonstrate the delicate pressure balance which existed between the right and left sides of this patient's heart. During exertion the shunt passed from right to left through a ventricular septal defect which might or might not have been associated with overriding of the aorta. It was possible to demonstrate the presence of a ventricular septal defect by catheterization but it was not possible to demonstrate clinically any overriding of the aorta. Since, as pointed out by Selzer,[8,9] mild degrees of overriding of the aorta may be difficult to detect even on direct anatomic examination, it seems reasonable that the clinical demonstration of this abnormality might prove impossible. Thus the congenital defects in Case III might be an example of the tetralogy of Fallot with minimal overriding of the aorta.

In general it has not been our practice to attempt correction of mild pulmonic stenosis. Furthermore, in patients with associated left to right intracardiac shunts it was considered possible that some degree of pulmonic stenosis might be a compensating mechanism controlling the degree of left to right shunt through the defect, and that correction of the stenosis might be detrimental by increasing the magnitude of the left to right shunt. These considerations have led us to question the advisability of operation on patients with pulmonic stenosis and left to right intraventricular shunts. Nevertheless, two handicapped patients were subjected to procedures of the Brock type because the pulmonic stenosis was considered severe. In both patients valvulotomes as well as the surgeon's finger were passed through the valvular area from the right ventricle, and in Case III an infundibular ridge was identified from which muscle was removed by a Brock punch. However, no pressure changes occurred in the right ventricle or pulmonary artery in either patient following these procedures. Therefore we are unable to draw conclusions regarding the effect of pulmonary valvulotomy in patients with pulmonary stenosis and left to right intraventricular shunts. Nevertheless, it might be wiser to defer operation in such patients until improved technics with direct visualization permit better reconstruction of the outflow tract and simultaneous closure of the septal defect. For the present, valvulotomy might be restricted to those patients with pulmonary stenosis, with marked elevation of the right ventricular pressure and without evidence of a predominant left to right intracardiac shunt.

SUMMARY

1. Data obtained in six patients with pulmonary stenosis and left to right intracardiac shunts of blood are presented. In four patients

there were coexisting ventricular septal defects, and in two patients atrial septal defects were demonstrated.

2. The factors governing the direction of the intracardiac shunts in such patients include the degree of pulmonary stenosis, the degree of compensation of the right ventricle and, in those with associated ventricular septal defects, the degree of dextroposition of the aorta.

3. In the four patients with pulmonary stenosis and left-to-right intraventricular shunts, a possible relationship to the tetralogy of Fallot has been considered.

4. A predominant left-to-right intracardiac shunt in the presence of pulmonary stenosis should be evaluated as a possible contraindication to valvulotomy.

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Tuberculosis and Congenital Cyanotic Heart Disease*

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THE relationship of tuberculosis and heart disease has been of interest to clinicians and pathologists for generations. Rokitansky and other observers[1–4] considered pulmonary tuberculosis to be uncommon in patients with mitral stenosis and this opinion is currently held by many clinicians. In contrast, pulmonary tuberculosis has been thought to occur frequently in patients with congenital pulmonary stenosis after the age of puberty.[5] We have recently studied a large number of patients with congenital cyanotic heart disease with a view to determining the incidence of pulmonary tuberculosis in this group.

We have studied not only the concomitance of these two conditions but also the effect on pulmonary tuberculosis of surgical measures designed to correct the congenital cyanotic heart disease. Two clinical cases exemplify this latter phase of the problem, which some of us have previously investigated in the experimental laboratory. In those studies we demonstrated that certain alterations in pulmonary circulation exert an adverse effect on the course of induced pulmonary tuberculosis in monkeys.[6–8] These results raised the disturbing possibility that operative alterations in the pulmonary circulation of patients with congenital cyanotic heart disease may result in activation of latent tuberculous foci in the lungs. Should this be so, one faces a perplexing problem in deciding on the therapy for cyanotic heart disease in the presence of advanced pulmonary tuberculosis.

On the basis of these clinical experiences and laboratory investigations we shall attempt to outline a rational basis for the therapy of patients with congenital cyanotic heart disease complicated by pulmonary tuberculosis.

RADIOLOGIC SURVEY AND CLINICAL STUDY

We have reviewed roentgenograms of the chest in over 1,000 patients with congenital pulmonary stenosis who were submitted to thoracotomy at The Johns Hopkins Hospital from November, 1944, to November, 1950. These patients were initially studied by Dr. Helen B. Taussig and her associates in the Cardiac Clinic of the Harriet I ane Home and subsequently operated on by Dr. Alfred Blalock and his staff. In this group there were 800 patients whose roentgenograms were suitable on critical examination for diagnostic evaluation of the pulmonary fields. These satisfactory roentgenograms were studied carefully for radiologic evidence of tuberculosis either of the primary or the reinfection type. Preoperative films were used as a basis for study because pleural and parenchymal changes after operation often make accurate evaluation difficult.

The unreliability of roentgenograms alone as a diagnostic criterion for tuberculosis is well recognized. Many other agents can produce a similar radiologic appearance which must be further elucidated by skin testing, sputum examination and cultures. However, if one arbitrarily considers parenchymal or hilar calcification to be representative of healed, primary tuberculous infection, any error will be in the direction of including more patients than should properly be considered tuberculous. Our primary interest was to insure against missing any patient with roentgenologic evidence compatible with pulmonary tuberculosis. Similarly, we considered cavitation or unexplained parenchymal infiltration, especially in the upper lung fields, to be representative of the reinfection type of tuberculosis, while recognizing fully that this is not the only cause of such radiologic changes.

The distribution of the 800 patients according to age and sex is shown in Table 1. As might be expected from the presenting cardiac lesion which makes itself apparent at an early age, three-quarters of these patients were under ten

* From the Department of Radiology of the Johns Hopkins University and the Departments of Surgery of St. Louis University and Vanderbilt University.

years of age. There were somewhat more males than females in the series. The patients came from all sections of this country as well as from abroad; only four of them were Negroes.*

The prevalence of primary tuberculosis in these 800 patients with pulmonary stenosis, as determined by the radiologic criteria outlined previously, is indicated according to age and sex in Table II. The occurrence of the reinfection type of pulmonary tuberculosis in these 800 patients is outlined in Table III. These tables may be summarized by saying that there were thirty-nine cases in which the radiologic findings were compatible with pulmonary tuberculosis. Twenty-two of these cases suggested the primary type of infection whereas the remaining seventeen showed radiologic evidence compatible with a reinfection type of tuberculosis. This represents an average of 4.87 per cent of the patients with congenital cyanotic heart disease who showed radiologic changes compatible with the diagnosis of tuberculosis.

Tuberculin tests were carried out on a number of these patients and an attempt was made to bring back those who had not been submitted to tuberculin testing at the time of their initial visit. In ten of the thirty-nine patients the tuberculin reaction is unknown. In the remaining twenty-nine there are twenty-four negative tuberculin tests and five positive tuberculin tests. Among the patients who showed radiologic evidence compatible with the primary type of tuberculosis (twenty-two patients) there were no positive tuberculin tests, fifteen negative tuberculin tests and seven patients in which the test was not carried out. In the seventeen patients in whom the radiologic evidence was compatible with the reinfection type of tuberculosis there were five positive tuberculin tests, nine negative tests and in two instances the test was not performed.

TABLE I

EIGHT HUNDRED OPERATIVE CASES OF PULMONARY STENOSIS: AGE AND SEX DISTRIBUTION OF CASES

Age in Years	Male	Female	Total	Per cent
0–4	180	125	305	38.1
5–9	162	127	289	36.1
10–14	64	40	104	13.0
15–19	33	21	54	6.8
20–24	17	5	32	4.0
25–29	6	5	11	1.4
30–34	3	2	5	0.6
0–34	465	335	800	100.0

TABLE II

EIGHT HUNDRED OPERATIVE CASES OF PULMONARY STENOSIS: PREVALENCE OF PRIMARY PULMONARY TUBERCULOSIS (*Radiologic Diagnosis Only*)

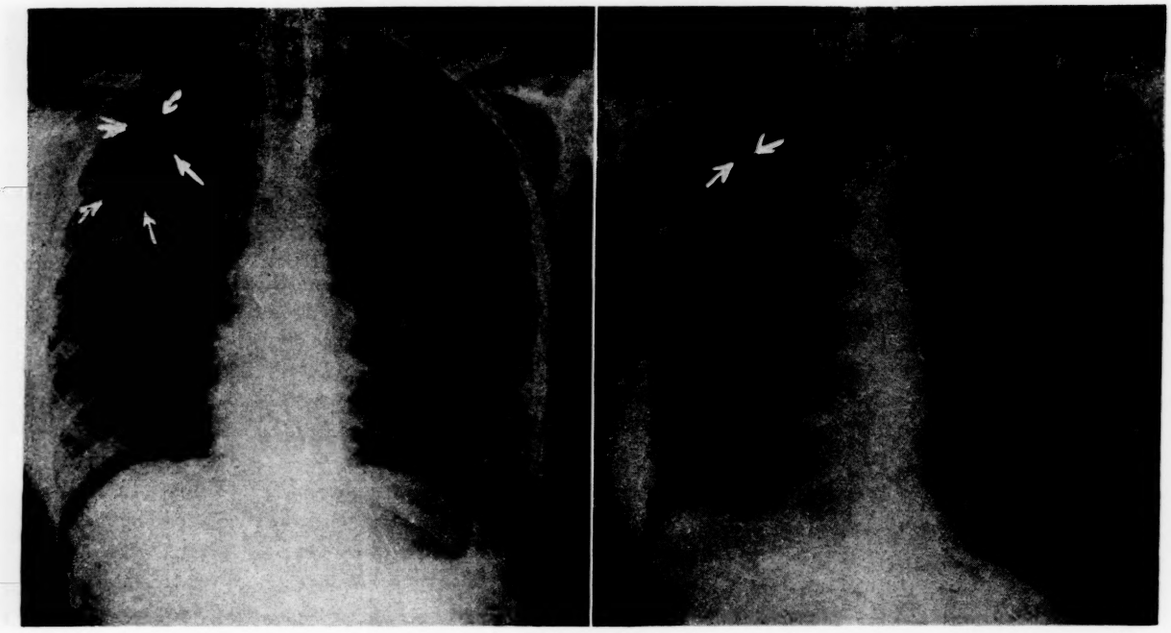
Age in Years	Male			Female		
	No. Observed	Primary Tuberculosis		No. Observed	Primary Tuberculosis	
		No. of Cases	Prevalence Ratio (%)		No. of Cases	Prevalence Ratio (%)
0–4	180	2	1.1	125	0	...
5–9	162	10	6.1	127	1	0.7
10–14	64	5	7.8	40	1	2.5
15–19	33	2	6.6	21	0	...
20–24	17	0	...	15	0	...
25–29	6	0	...	5	1	20
30–34	3	0	...	2	0	...
Age 0–34	465	19	4.1	335	3	0.9

TABLE III

EIGHT HUNDRED OPERATIVE CASES OF PULMONARY STENOSIS: PREVALENCE OF REINFECTION PULMONARY TUBERCULOSIS (*Radiologic Diagnosis Only*)

Age in Years	Male			Female		
	No. Observed	Reinfection Pulmonary Tuberculosis		No. Observed	Reinfection Pulmonary Tuberculosis	
		No. of Cases	Prevalence Ratio (%)		No. of Cases	Prevalence Ratio (%)
0–4	180	0	....	125	0	....
5–9	162	0	....	127	0	....
10–14	64	1	1.6	40	0	....
15–19	33	2	6.1	21	0	....
20–24	17	8	47.0	15	3	20.0
25–29	6	1	16.7	5	0	....
30–34	3	2	66.7	2	0	....
Ages 0–34	465	14	3.0	335	3	0.9
Ages 15–34	59	13	22.0	43	3	6.9

* During the six-year period in which these 800 patients with pulmonary stenosis were submitted to operation, a large additional group of congenitally cyanotic patients was examined in the Cardiac Clinic of the Harriet Lane Home in which surgery was delayed or considered inadvisable for various reasons. In only one instance was flagrant pulmonary tuberculosis found to be the condition contraindicating surgery. This twenty-four year old man with tetralogy of Fallot and bilateral pulmonary tuberculosis died from extension of the tuberculosis several months after his visit to the Clinic.



1 2

FIG. 1. Case 1. Roentgenogram of chest showing large cavity in right upper lobe one year before operation for pulmonary stenosis.

FIG. 2. Case 1. Roentgenogram of chest three years after end-to-end subclavian-pulmonary anastomosis on left. Persistent small cavity in posterior segment of right upper lobe prompted segmental resection.

While admitting freely that these data are unsatisfactory and incomplete, it appears justifiable to state that the incidence of pulmonary tuberculosis among this large group of patients with congenital cyanotic heart disease does not appear to be excessively high. Even if one makes the unlikely assumption that all of the patients in whom the tuberculin test was not done had in fact a positive reaction, this would result in a positive tuberculin reaction in only fifteen of the thirty-nine cases in whom the radiologic examination suggested pulmonary tuberculosis. One might fairly state that the maximum possible incidence by these criteria was well under 2 per cent.

Two of the thirty-nine cases are of particular interest since they represent flagrant clinical examples of tuberculosis. Before presenting these cases in detail it might be pertinent to mention the fact that follow-up studies on the other thirty-seven patients have shown no evidence of activation of what might be considered to be a latent tuberculous focus. The significance of this observation will be discussed in connection with a review of the effect of experimental anastomoses on tuberculosis. The detailed case reports are as follows:

CASE 1. A. J., a twenty-three year old white female, was admitted to The Johns Hopkins Hospital in May, 1950, because of congenital cyanotic heart disease and pulmonary tuberculosis. Cyanosis, exertional dyspnea and easy fatigability had been present since infancy. One year before admission she had been studied in the Cardiac Clinic where cardiac findings suggested tricuspid atresia. A large cavity was found in the right upper lobe. (Fig. 1.) Sputum was positive for M. tuberculosis. The patient was sent to a sanatorium where she remained on a regimen of bed rest. Attempted pneumothorax was unsuccessful. After a few months in the sanatorium the sputum became negative and there was progressive diminution in the size of the cavity. She was started on streptomycin and PAS several weeks before transfer to the hospital.

Examination on entry revealed a well developed and well nourished young woman with intense cyanosis of skin, mucous membranes and nail beds and clubbing of fingers and toes. Lungs were clear to auscultation and percussion. Heart was small, rhythm was regular, pulse rate 80, blood pressure 110/85. There was a soft systolic murmur over the precordium. An electrocardiogram showed a right axis deviation.

Fluoroscopy revealed a small heart which was rotated to the right. The lung fields appeared avascular; there was considerable fibrosis surrounding a 3 cm. cavity in the right upper lobe. Routine laboratory findings were within normal limits except for polycythemia.

Operation was carried out on May 13, 1950, under intratracheal cyclopropane anesthesia. The left chest was entered anteriorly. The left lung showed no gross evidence of tuberculosis. Accordingly, the left pulmonary artery was ligated centrally and divided. Anastomosis was then made between the end of the left subclavian artery and the distal end of the left pulmonary artery.

The immediate postoperative course was essentially uneventful. The patient's color was improved and there was no spread of tuberculosis. Three weeks after operation she was discharged to her home for continued bed rest, streptomycin and PAS under the care of her local physician. After several months this regimen was discontinued and a gradual return to ambulatory status was permitted.

During the next two years she was much improved, with no cough, sputum or dyspnea. Serial films of the chest showed complete disappearance of the cavity. Her color improved until only slight cyanosis of nail beds persisted and exercise tolerance was much increased.

In July, 1952, following an upper respiratory infection, she became febrile, the cavity reopened and sputum became positive. She reentered the sanatorium promptly and treatment with bed rest, streptomycin, PAS and isoniazid was instituted. Because of persistence of the cavity excisional surgery was believed indicated. (Fig. 2.)

On March 22, 1953, she was admitted to the Vanderbilt University Hospital for lobectomy. Examination showed her color to be good except for residual cyanosis of nail beds. The nutritional state was excellent. The lungs were clear to clinical examination. There was no cardiac enlargement. A soft, blowing, continuous murmur was audible to the left of the sternum. Laminograms demonstrated a multiloculated cavity in the posterior segment of the right upper lobe. Bronchoscopy was negative. Hemoglobin was 17 gm. per cent with hematocrit of 56 per cent.

On March 24, 1953, right posterolateral thoracotomy was carried out under intratracheal cyclopropane anesthesia and resection of the apical and posterior segments of the right upper lobe was performed. Large numbers of vascular collaterals were encountered, with copious bleeding from the chest wall which was controlled with difficulty. Despite massive blood replacement the patient died about ten hours after operation.

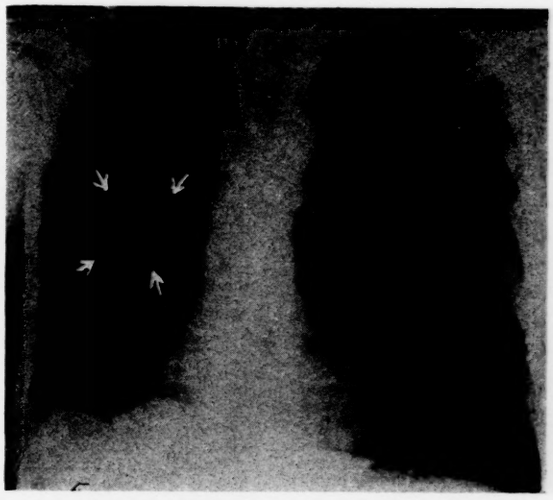


FIG. 3. Case II. Roentgenogram of chest in patient with tetralogy of Fallot prior to thoracoplasty in another institution. Persistence of cavity beneath thoracoplasty prompted right pneumonectomy combined with anastomosis between end of right subclavian artery and central end of right pulmonary artery.

Autopsy showed a right hemothorax with compression atelectasis of the right lung. There were no gross tuberculous lesions in either right or left lung except in the excised apical and posterior segments. The end-to-end anastomosis between left subclavian and left pulmonary arteries was widely patent. The heart showed a single ventricle with a normal aorta and a narrow, hypoplastic pulmonary artery arising from the base of the ventricle. There was no rudimentary outlet chamber. Both atria, atrial septum and atrioventricular valves were anatomically normal.

Comment. Surgical relief of pulmonary stenosis in this patient with a tuberculous cavity in the right lung was accomplished by performing an end-to-end subclavian-pulmonary anastomosis on the left. "Arterialization" of the lung containing the tuberculous focus was thus avoided and a satisfactory cardiac result was obtained. The tuberculous lesion in the right lung remained stable for two years following the anastomosis.

CASE II. V. R., a twenty-one year old white

male, was admitted to The Johns Hopkins Hospital on March 18, 1951, because of congenital cyanotic heart disease and pulmonary tuberculosis. Cyanosis and limited exercise tolerance had been present since birth. He was able to walk only short distances and was greatly incapacitated. In 1945 he was found to have pulmonary tuberculosis. Because of a persistent cavity in the right hilar region (Fig. 3) and positive sputum a thoracoplasty was performed in 1950. This did not result in complete closure of the cavity, however, or in sputum conversion.

Examination on admission revealed a thin, intensely cyanotic young man with a moderately severe kyphoscoliosis, a right posterolateral thoracoplasty scar and attendant deformity of the chest wall and clubbing of fingers and toes. Breath sounds were diminished on the right. There was no detectable cardiac enlargement. Cardiac rhythm was regular, rate 84, blood pressure 110/80. There was a loud systolic murmur over the entire precordium.

Fluoroscopic and radiologic studies of the chest showed the heart to have the typical characteristics of tetralogy of Fallot. The left lung field was clear and avascular. There was partial collapse of the right lung with extensive fibrotic changes in the hilar and mid-lung areas. Laminograms revealed a small cavity in the hilar region on the right.

Routine laboratory studies were within normal limits except for manifestations of polycythemia. Twenty-four hour sputum collections were negative on smear and positive on culture for M. tuberculosis. The electrocardiogram showed right axis deviation. Bronchoscopy showed no evidence of laryngeal or endobronchial disease. Bronchospirometric studies showed the right lung to contribute 29 per cent and the left lung 71 per cent of the patient's vital capacity.

The patient was given streptomycin and PAS in preparation for operation. After prolonged consideration of his problem it was decided to perform anastomosis between the end of the right subclavian artery and the central end of the right pulmonary artery and to remove the right lung.

Operation was carried out on March 28, 1951, under intratracheal cyclopropane anesthesia. An anterior thoracotomy incision was placed on the right and the chest entered through the bed of the regenerated third rib. There were diffuse fibrous adhesions and numerous vascular collaterals which made dissection difficult and tedious. The adherent lung was freed from the mediastinum. The right pulmonary artery was secured centrally with a Blalock clamp, ligated distally and divided. The proximal end of the right subclavian artery was turned down in apposition to the right pulmonary artery. Anastomosis was then performed between the end of the right subclavian and the central end of the right pulmonary artery. The patient's color improved promptly. The right pulmonary veins and the right bronchus were then divided and sutured. The lung was densely adherent to the chest wall and despite extrapleural mobilization it could be removed only with great difficulty. Bleeding from the chest wall was profuse and could never be controlled satisfactorily. Despite massive blood replacement the patient died in shock about four hours after operation.

Autopsy showed a massive hemothorax on the right. The cardiac malformation was a typical tetralogy of Fallot with infundibular stenosis. The subclavian-pulmonary anastomosis was intact. The left lung was quite normal throughout with no demonstrable tuberculous foci in it. The surgically excised right lung was contracted and fibrotic and contained numerous small solid caseous lesions and one small cavity in the hilar region. Acid-fast bacilli and tubercles were demonstrated in these areas on histologic study.

Comment. Surgical management of this difficult combination of pulmonary stenosis and tuberculous cavity persisting in the collapsed right lung under a thoracoplasty was planned in such a way as to increase pulmonary blood flow and yet to avoid "arterialization" of the lung containing the cavity. Anastomosis between the right subclavian artery and the central end of the divided right pulmonary artery was designed to increase the blood flow to the left lung. Right pneumonectomy was carried out at the same time since a hilar cavity persisted despite previous thoracoplasty in a lung with greatly impaired respiratory function. Furthermore, if the right lung had been left *in situ* following the subclavian-pulmonary anastomosis it would have been totally "arterialized"; its pulmonary artery had been interrupted and it would have been perfused only by systemic arterial blood via the bronchial system and the collaterals. Consideration of left thoracotomy and end-to-end subclavian-pulmonary anasto-

mosis on the left as an alternative was deemed unwise because of the inadequate functional capacity of the collapsed right lung.

OBSERVATIONS

From the data cited earlier in this presentation it appears that the incidence of pulmonary tuberculosis in patients with congenital cyanotic heart disease is not strikingly high. Moreover, we have no convincing evidence from the clinical data at hand to suggest that surgical therapy increases the risk of concomitant tuberculosis in these patients.* The usual surgical therapy has consisted of anastomosing one of the aortic branches to one of the pulmonary arteries in an end-to-end or an end-to-side fashion.[9]

Our experimental work in monkeys infected with tuberculosis has demonstrated a distinctly unfavorable result which occurs when a tuberculous lung is perfused with systemic arterial blood.[6-8] Presumably it is the "arterialization" of the infected pulmonary tissue which results in aggravation of the infection. Such a result is in keeping with the observation that the growth of tubercle bacilli *in vitro* is enhanced by high oxygen concentration.[10,11] One might predict *a priori* that a systemic-pulmonary arterial anastomosis would worsen the pulmonary tuberculous lesions in *both* lungs with an end-to-side anastomosis, or in the "arterialized" lung with an end-to-end anastomosis.

If the physiologic problem in pulmonary stenosis of the type accompanying tetralogy of Fallot is inadequate blood flow to the lungs, how may one best increase this blood flow without risking exacerbation of a coexistent pulmonary tuberculosis? Assuming that an end-to-end anastomosis on the side with more tuberculosis will be highly inadvisable, several other possibilities present themselves. One may perform an end-to-end anastomosis on the side opposite the major tuberculous involvement, as in Case I. This will increase pulmonary blood flow, raise the peripheral arterial oxygen saturation and improve the exercise tolerance without "arterialization" of the lung which harbors the major tuberculous focus. Similarly, an end-to-side anastomosis on the side opposite the major tuberculosis involvement might be satisfactory because the systemic arterial blood in such anastomoses may be directed principally to the lung on the side of the anastomosis, forming in effect an end-to-end union.

Alternatively, the direct (Brock) attack on the point of intracardiac obstruction might be performed which would increase the blood flow to both lungs without raising the oxygen saturation of the perfusing blood.[11]

Finally, as in the second case previously described, one might perform an end-to-end (or end-to-side) anastomosis on the side of the major tuberculous involvement, followed by a resection of the appropriate amount of involved pulmonary tissue. This may be a formidable technical problem, as illustrated by the case report cited.

It is apparent that the results of experimental work in monkeys with induced tuberculosis cannot be employed unreservedly in a judgment of the clinical problem presented by coexisting pulmonary tuberculosis and congenital cyanotic heart disease associated with a form of pulmonary stenosis. Aside from the obvious species differences and the possible variation in type of pulmonary tuberculous infection, it is obvious that the lung in tetralogy of Fallot shows certain vascular changes peculiar to the disease.[12] In the experimental monkey, moreover, fully oxygenated blood is allowed to perfuse the infected lung, while in congenitally cyanotic patients with tetralogy of Fallot the blood in the aortic branches can never reach full oxygen saturation because of the interventricular septal defect and overriding aorta. It is obvious therefore that these observations must be considered largely speculative even though they appear to be based on much reliable information.

It has been noted in the discussion of age and sex distribution among these 800 patients that most of them (74.8 per cent) are below the age of ten years. This renders the expected incidence of tuberculosis much less than in an older age group; indeed, the patients with radiologic and tuberculin test findings compatible with tuberculosis are largely in the age group from fifteen to thirty-four. It is possible that the incidence of florid pulmonary tuberculosis may increase significantly as these treated patients reach the older age groups, especially since many are carrying a systemic-pulmonary artery shunt which theoretically furnishes favorable conditions for aggravation of pulmonary tuberculosis.

* Dr. E. B. Mahoney of Rochester, N. Y., has informed us that he has a thirteen year old patient with tetralogy of Fallot who developed a rapidly advancing tuberculous lesion in the right upper lobe a few weeks after the performance of end-to-side subclavian-pulmonary anastomosis on the left. Right upper lobectomy was subsequently done with success.

Further clinical observation over many years may clarify this point.

SUMMARY

In an attempt to ascertain the incidence of pulmonary tuberculosis among patients with congenital cyanotic heart disease, we have reviewed the roentgenograms of the chest of 800 patients who were submitted to operation for pulmonary stenosis.

Thirty-nine of these patients presented radiologic findings consistent with pulmonary tuberculosis. Further study of these thirty-nine patients, including tuberculin tests, excluded tuberculosis in twenty-four instances. In the 800 patients the maximal possible incidence of tuberculosis by these criteria is less than 2 per cent.

The experimental work on aggravation of induced pulmonary tuberculosis by circulatory alteration in the lung is reviewed. In the light of this work we have briefly discussed the most suitable operative procedures for correction of congenital cyanotic heart disease complicated by pulmonary tuberculosis. The recommendations are illustrated by two detailed case reports.

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Bacterial Endocarditis*

An Analysis of Fifty-two Cases

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ABOUT thirty-five years ago Libman[1] and Blumer[2] and later Libman and Friedberg,[3] suggested the following as diagnostic criteria for subacute bacterial endocarditis: (1) Persistent fever, (2) valvular deformity, congenital cardiac lesion or arteriovenous aneurysm as indicated by organic murmurs, bruits and associated phenomena, (3) embolic and vascular lesions, notably emboli of major arteries, white-centered petechiae or Osler's nodes and (4) positive blood cultures. Although these manifestations were not usually found early in the course of the disease, therapeutically it mattered little whether the diagnosis was established early or late. One could only hope that the patient under observation might fall in the group of so-called spontaneous recoveries[3] which occurred in about 3 per cent of the cases of bacterial endocarditis.

When the sulfa drugs[4,5] and later penicillin[6–11] and the mycins[12–15] were shown to be effective in curing the infection, the urgency for early diagnosis became apparent. Wilkinson obtained the best results in patients with bacterial endocarditis treated early[11] and Friedberg noted that the largest percentage of therapeutic failures occurred in patients treated late.[16] In 1948 Christie[17] found a 34 per cent mortality rate in patients treated within six months of onset of the disease whereas death occurred in over 60 per cent of those infected for more than six months before treatment was started. Moreover, the increased cardiac damage resulting from scarring and distortion of the valves on healing[18–21] might be lessened, if not prevented, by treatment in the early stage of the disease, as valvular involvement might still be slight and healing might not result in as much valvular deformity.

As earlier institution of treatment required earlier diagnosis, Friedberg in 1950[16] proposed that unexplained fever for more than one week in patients with an organic cardiac murmur or arteriovenous fistula be considered sufficiently suspicious of bacterial endocarditis to justify institution of therapy. He objected to dependence on positive blood cultures before instituting treatment and also advised against waiting for the appearance of embolic phenomena, for embolism denoted advanced disease. Some of our cases of bacterial endocarditis not only lend support to Friedberg's proposal but also have provided us with unusual experiences which have led us, in certain instances, to become aware of the disease even in the absence of fever.

MATERIAL

From August, 1946, to January, 1953, fifty-two cases of proven bacterial endocarditis were admitted to the Bronx Veterans Administration Hospital. The cases presented in this series had either positive blood cultures while alive or on autopsy demonstrated the characteristic pathology of bacterial endocarditis. We did not attempt to divide our cases into acute and subacute varieties since we have found that organisms considered to give rise to the acute type occasionally ran a subacute clinical course. Conversely, we have seen occasional cases infected with the alpha-streptococcus whose clinical course was acute. Moreover, it would be misleading to classify cases according to duration of symptoms since treatment, by prolonging the span of the disease, would render one unable to tell which were supposed to be acute or subacute.[22]

DIAGNOSIS

Of the fifty-two cases twelve were admitted to the hospital with the correct diagnosis. In the remaining forty the most common admission diagnoses in order of frequency were: rheumatic heart disease, fever of unknown etiology, renal

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disease, malaria and acute rheumatic fever. On discharge the correct clinical diagnosis was established in thirty-seven cases, suspected in seven cases and, up to the time of autopsy, neither diagnosed nor suspected in eight cases. The four most common findings in order of frequency were audible murmurs, fever, anemia and positive blood cultures. (Table I.) Although the duration of the infection prior to treatment has been reported to be a significant factor affecting prognosis,[23] we did not subdivide the incidence of symptoms according to the duration of the disease as the number of patients in our series who had symptoms for more than six months prior to treatment was not statistically significant. Only twenty-four of our fifty-two proven cases of bacterial endocarditis fulfilled the original criteria of Libman,[1] Blumer[2] and Libman and Friedberg.[3]

TABLE I
SIGNIFICANT FINDINGS IN ORDER OF INCIDENCE IN FIFTY-TWO PROVEN CASES OF BACTERIAL ENDOCARDITIS

Manifestations		Per cent
Major		
Murmur heard	48/52	92
Fever	44/52	85
Anemia	42/52	81
Positive blood culture*	32/48	67
Minor		
Palpable spleen	26/52	50
Petechiae	23/52	44
Clubbing	21/52	40
Microscopic hematuria	17/52	33
Arterial emboli	15/52	29
Osler's nodes	5/52	10

* No blood cultures were taken in four cases. Blood cultures were positive in three afebrile cases. Two cases were afebrile with negative blood cultures and had no clubbing, splenomegaly or anemia.

Contrary to other reports,[24] it would appear from the data in Table I that the presence of an audible murmur is practically a *sine qua non* for the diagnosis of bacterial endocarditis. Of the four patients in whom no murmurs were heard, one had the disease implanted and localized on a normal tricuspid valve, another developed a murmur after therapy was started and in the third and fourth cases the patients had severe hypertensive and arteriosclerotic heart disease, were critically ill and had associated tachycardia and gallop rhythm which could have masked significant murmurs.

Since murmurs, fever, anemia and positive blood cultures occurred in the majority of our cases, these may be considered to be the major clinical manifestations of bacterial endocarditis. The remainder of the signs listed in Table I, from the point of view of incidence, may be considered as minor manifestations since none of these occurred clinically in more than half of the cases. If we consider the presence of an audible murmur associated with another major or two minor manifestations as indicative of the disease, the correct clinical diagnosis in our series could have been made in forty-seven of the fifty-two cases. The obvious objection to using these criteria is that it would include many patients who do not have the disease, unless one observes extreme caution in the evaluation of such non-specific signs as fever and anemia. Using these criteria, the correct diagnosis could have been made in two of our eight cases in which the disease was not suspected during life.

There are certain clinical phenomena which are said to be rare in the presence of bacterial endocarditis, namely, established auricular fibrillation[3,25,26] and congestive heart failure anteceding the infection. Four of our fifty-two patients had established auricular fibrillation anteceding the onset of their bacterial endocarditis; four developed transient auricular fibrillation during the course of their infection. Thirty-four patients had congestive heart failure. Of these five had established congestive heart failure at least two years before the onset of the bacterial endocarditis and twenty-nine developed congestive heart failure during the course of their disease. In eight congestive heart failure was an initial manifestation.

Weight loss and malaise were present in forty-seven of the fifty-two patients and the sedimentation rate was normal in only nine patients. Leukocytosis and albuminuria, though generally present, were of low grade. Hyperglobulinemia and arthralgia were each found in only five cases.

THERAPY

Since our cases were not treated under a given protocol and some of them date back to 1946, the choice of antibiotics, dosage and duration of therapy varied widely. Thus to evaluate our cases from this viewpoint we arbitrarily chose as

a minimum dosage 1.2 million units of penicillin or 3 gm. of aureomycin, terramycin or chloramphenicol daily for at least two weeks. Although we do not consider this the ideal dosage schedule (the majority of our patients received much more therapy), in order to evaluate data such as cure rate, a minimum schedule which cured patients with subacute bacterial endocarditis had to be chosen. Hamburger and Stein[27] have recently indicated that two-week courses of therapy may be adequate. On this basis thirty-nine of our patients received adequate treatment.

TABLE II
FIFTY-TWO CASES OF PROVEN BACTERIAL ENDOCARDITIS 1946–53

Untreated or inadequately treated: 13
Adequately treated: 39
  Died with refractory infection: 12
  Cured infection: 27 (cured-infection rate 69%)
    Died with congestive heart failure: 9
    Asymptomatic: 9
    Alive but disabled: 9
      Embolic residua: 2
      Congestive heart failure: 6
      Renal disease: 1

By all available criteria for cure, the cured-infection rate in our series was 69 per cent. Of the twenty-seven patients cured of their infection, one-third died from sequelae of the disease, one-third are alive but disabled and one-third are alive and asymptomatic. (Table II.) The length of follow-up in our eighteen living patients is noted in Table III.

TABLE III
LENGTH OF FOLLOW-UP IN EIGHTEEN LIVING CASES

Time	No.
6 mo–1 year	7
1–2 years	4
2–3 years	3
3–4 years	2
4–5 years	2

It seemed to us that certain factors might be important in determining the curability of a case of bacterial endocarditis. Therefore in our twelve patients who were adequately treated but died with refractory infection we investigated the following features: (1) duration of disease from onset to time when adequate therapy was instituted, (2) drugs and dosage used in therapy and duration of therapy, (3) previous inadequate antibiotic therapy, (4) responsible organism and (5) sensitivity studies on responsible organism. When these factors were evaluated and compared to the twenty-seven adequately treated and apparently cured patients, the following observations were noted:

1. *Duration of Disease from Onset to Time Adequate Therapy Was Instituted.* The disease was manifest before adequate therapy was instituted for an average of nine weeks in the twelve patients dying with refractory infection and ten weeks in the twenty-seven patients cured of their infection. This difference is not statistically significant and it would therefore seem from our observations that duration of disease prior to onset of adequate therapy, if less than six months has no detectable effect on the refractoriness of the infection. This conclusion does not negate the observation of Cates and Christie[23] who state that mortality is greater in those infected for six months or more, since only four of these thirty-nine patients were infected for that period of time. Nor should this observation be construed to mean that duration of disease prior to onset of adequate therapy has no effect on the final outcome, since we have not correlated this factor with such things as the appearance of congestive heart failure, embolic phenomena and renal insufficiency.

TABLE IV
RESPONSIBLE ORGANISMS IN THIRTY-NINE ADEQUATELY TREATED CASES

	Infection Cured	Refractory Infection
Negative blood cultures	6	5
Alpha-streptococcus	16	2
Non-hemolytic gamma streptococcus	2	0
Non-hemolytic staphylococcus albus	1	1
Hemolytic staphylococcus albus	1	1
Staphylococcus aureus	1	1
Salmonella enteritidis	0	1
Pseudomonas aeroginosa	0	1
Totals	27	12

2. *Drugs and Dosage Used in Therapy and Duration of Therapy.* Of the twelve patients who died with refractory infection, six received optimum therapy even in the light of present day knowledge, the other six, however, did not receive what would now be considered adequate therapy.[28] However, many of the cured cases received no more therapy than these latter six treatment-failures so that no comparative statement can be made.

3. *Previous Inadequate Antibiotic Therapy.* There was a history of inadequate and sporadic antibiotic therapy prior to admission in eighteen of our twenty-seven cured patients (67 per cent) and in seven of our twelve patients (58 per cent) who died of refractory infection. Thus it would seem that the use of inadequate dosage of antibiotics for short periods of time does not appear to affect the cure rate of bacterial endocarditis significantly.

TABLE V

TOTAL NO. OF FATALITIES: THIRTY-FOUR

Adequately treated cases: 21/39 (mortality rate—54%)
  Due to refractory infection: 12
  Due to congestive heart failure: 9
Inadequately or untreated cases: 13/13 (mortality rate—100%)
Autopsy rate: 31/34 (91%)

4. *Responsible Organism.* Examination of Table IV reveals, in the refractory cases, a low incidence of infection with alpha streptococcus, a relatively high incidence of negative blood cultures and two cases of infection with gram-negative organisms which notoriously are resistant to therapy.[16]

5. *Sensitivity Studies.* There are insufficient data in our series to justify any statement regarding the sensitivity of the organisms in these two groups of cases.

MORTALITY STUDIES

Thirty-four of our fifty-two patients died. (Table V.) All thirteen of the untreated or inadequately treated patients died. Of the thirty-nine adequately treated patients twenty-one died, twelve with a refractory infection and nine with a cured infection but refractory congestive heart failure. Thus the over-all mortality rate for the series was 34/52 or 65 per cent. In the untreated or inadequately treated patients the mortality rate was 13/13 or 100 per cent. The mortality rate in the adequately treated patients was 21/39 or 54 per cent. Of the twenty-seven patients cured of their infection, nine died of congestive heart failure, giving a mortality rate of 33 per cent in those patients cured of their infection.

Of the thirteen patients who were untreated or inadequately treated, all but one were autopsied. One of these cases had spontaneous healing of the subacute bacterial endocarditis at autopsy. Death was due to congestive heart failure in six of the patients, to uremia in two, to uremia and congestive heart failure in three and to carcinoma in two.

Of the twenty-one deaths in patients treated adequately for their infection, twelve died with a refractory infection and nine died with a cured infection. The causes of death in the twelve patients who died with a refractory infection were: congestive heart failure in six, uremia and congestive heart failure in three and miscellaneous causes in three. Eleven of these twelve cases were autopsied. In the nine patients whose infections were cured, all died with congestive heart failure but without renal involvement; eight of the nine cases were autopsied.

RENAL INVOLVEMENT

We found evidence clinically and pathologically of renal insufficiency in eight patients, all of whom died with an active infection. In none of the patients who died with a cured infection, was there clinical evidence of renal insufficiency at the time of death. In the eighteen patients who were cured of their infection and are still living, only one has evidence of renal insufficiency attributable to bacterial endocarditis. This patient has been followed for twenty-eight months since the onset of his disease. In the thirty-nine adequately treated patients, seven showed transient clinical evidence of renal involvement which cleared with antibiotic therapy.

The lesions in the kidneys of the eight patients who died with renal insufficiency were as follows: two of the patients had focal embolic glomerulonephritis; one had diffuse glomerulonephritis; one had diffuse glomerulonephritis and multiple renal infarcts; two had diffuse glomerulonephritis, focal embolic glomerulonephritis and multiple renal infarcts and one had bilateral pyelonephritis and multiple renal infarcts.

Six of the autopsied cases had renal infarcts which clinically had manifested themselves with transient urinary abnormalities or mild nitrogen retention. One of the autopsied cases had focal embolic glomerulonephritis but was not uremic at the time of death, transient blood urea nitrogen elevation during his hospital course and persistent albuminuria with microscopic hematuria.

The figures for the average duration of the disease prior to onset of adequate therapy or death in those patients who died with renal insufficiency, when compared with those in patients without evidence of renal insufficiency, were not statistically valid since the number

of patients dying with renal insufficiency was too small and the scatter was too great.

CONGESTIVE HEART FAILURE

Thirty-four of our fifty-two patients had congestive heart failure. (Table VI.) In five of these patients the congestive heart failure anteceded the bacterial endocarditis. Eight of these patients developed congestive heart failure apparently as the first symptom of their bacterial endocarditis. The remaining twenty-one patients developed congestive heart failure during the course of their bacterial endocarditis.

TABLE VI

CASES OF BACTERIAL ENDOCARDITIS WITH CONGESTIVE HEART FAILURE: THIRTY-FOUR

1. Congestive heart failure anteceding the bacterial endocarditis: 5
   - (a) Inadequate or no therapy for bacterial endocarditis: 3
     - All died with congestive heart failure and active infection
   - (b) Adequate therapy: 2—both cured of bacterial endocarditis
     - 1 died of cerebral hemorrhage
     - 1 alive
2. Congestive heart failure as initial manifestation of bacterial endocarditis: 8
   - (a) Inadequate or no therapy: 5
     - All died with congestive heart failure and active infection
   - (b) Adequate therapy: 3
     - All cured of bacterial endocarditis but died with congestive heart failure
3. Congestive heart failure developing during course of bacterial endocarditis: 21
   - (a) Adequate therapy: 18 (cured-infection rate 10/18—56%: mortality rate 13/18—72%)
     - (1) Refractory infection: 8
     - (2) Cured infection: 10
       - (a) 5 died with congestive heart failure
       - (b) 5 alive but disabled with congestive heart failure
   - (b) Inadequate or no therapy: 3
     - All died with congestive heart failure and active infection

It is of interest to note that thirteen of our fifty-two patients had congestive heart failure either anteceding the onset of their bacterial endocarditis or as the initial manifestation of their disease. Of these thirteen, twelve died during their hospitalization and only one has been cured and is alive. Eight of these thirteen patients were untreated or inadequately treated either because they were in the hospital too short a period of time before they died or because the presence of congestive heart failure led the clinician not to consider bacterial endocarditis as a serious diagnostic possibility. Five of these patients were adequately treated and all were cured of their infection but only one survived.

Twenty-one patients developed congestive heart failure during the course of their bacterial endocarditis. Three patients were untreated or inadequately treated and died during hospitalization. Eighteen patients received adequate therapy for their bacterial endocarditis, five of these were cured and are alive, another five were cured of their infection but died with congestive heart failure and eight died with a refractory infection. Thus the cured-infection rate for this group was 56 per cent (10/18) but the death rate without counting untreated cases was 13/18 (72 per cent).

If one compares the average duration of the disease from its onset to the time of adequate therapy or death in the twenty-one patients who developed congestive heart failure during the course of their bacterial endocarditis, with the eighteen patients of the series who never developed congestive heart failure, there is no statistical difference.

If one compares the valve involved with bacterial endocarditis in the patients who never developed congestive heart failure with those who did develop it, one finds that the aortic valve was involved alone in 44 per cent of the patients who never developed congestive heart failure and in 62 per cent of those who did develop it. (Table VII.) The mitral valve was involved alone or in combination with the aortic valve in 50 per cent of the patients who never developed congestive heart failure, and in 33 per cent of the patients who did develop congestive heart failure after the onset of their subacute bacterial endocarditis.

BLOOD CULTURES

Blood cultures were taken in forty-eight of our fifty-two cases. Daily cultures were taken in some cases for fifteen to twenty days, and in not one did we get a positive culture after the fourth, if the first four were negative. Thirty-two of the patients (67 per cent) had positive blood cultures before treatment was started and all of these had at least one positive culture in the first four that were taken. Eight of this group with multiple cultures before treatment was instituted had intermittently positive blood cultures; the remaining twenty-four had consistently positive blood cultures before treatment was instituted. Of particular interest in this group of patients

with positive blood cultures are three cases who were afebrile.

One might wonder about the effect of antibiotic therapy on the chances of obtaining a positive blood culture. Twenty-six of our patients had inadequate and sporadic antibiotic therapy before admission to the hospital and of this group 77 per cent had positive blood cultures on admission. On the other hand, of twenty-two patients who did not receive any antibiotic therapy prior to admission, 68 per cent had a positive blood culture on admission.

TABLE VII

Valve Involvement in Relation to Congestive Heart Failure	Aortic		Mitral		Aortic and Mitral		Tricuspid		Total
No congestive heart failure	8/18	44%	4/18	22%	5/18	28%	1/18	6%	18
Congestive heart failure after bacterial endocarditis	13/21	62%	4/12	19%	3/21	14%	1/21	5%	21
Congestive heart failure before bacterial endocarditis	7/13	53%	1/13	8%	5/13	39%	0/13	0%	13
Totals:	28/52	54%	9/52	17%	13/52	25%	2/52	4%	52

COMMENT

Although we have no proof we believe that duration of the disease is an important factor in the development of embolization and congestive heart failure in bacterial endocarditis. Therefore, despite the fact that the statistical evidence would seem to indicate that the cure rate for this disease is unaffected by its duration within a six-month limit, we believe that early diagnosis and early institution of therapy is of paramount importance. All patients who, by virtue of a cardiac or vascular lesion, are potential candidates for bacterial endocarditis should be evaluated as follows: If the patient has had his underlying disease for a number of years and the situation has been static, a negative examination for fever, clubbing, splenomegaly, petechiae, Osler's nodes, anemia and microscopic hematuria should suffice to rule out bacterial endocarditis. On the other hand, if one or more of these findings are noted and not adequately explained by disease other than bacterial endocarditis, we believe that four blood cultures should be taken on successive days and the patient started on therapy for bacterial endocarditis without waiting for the results of the blood cultures. We do not consider that the presence of established auricular fibrillation, congestive heart failure, luetic aortic insufficiency or inferential evidence of severely damaged valves should lower the index of suspicion of bacterial endocarditis. There is only one finding which is often quoted as not occurring in bacterial endocarditis and which we did not find in our cases, namely, a pericardial friction rub.

We fully realize that with these criteria patients who do not have the disease will be treated for bacterial endocarditis. However, if we wish to return more patients to an asymptomatic state and to increase the survival rate, we must have a very high index of suspicion for this disease even if this means treating some patients unnecessarily. The risk that penicillin therapy carries is so small that it is not as dangerous to treat an individual who does not harbor the infection as it is to leave a patient untreated because it is believed that more evidence for bacterial endocarditis is necessary.

It would seem from our observations that the sporadic use of inadequate antibiotic therapy does not influence adversely the eventual curability of the disease. We would again like to emphasize that although we were able to "cure" 69 per cent of our patients of bacterial endocarditis, one-third of those "cured" died of congestive heart failure and one-third are alive but disabled from residua of the disease. Thus we were able to return to an asymptomatic state only 23 per cent of our adequately treated cases.

Our observations are in agreement with those of others[6,29] that the bacteriologic cure of this disease has a beneficial effect on the renal lesions capable of causing renal insufficiency in bacterial endocarditis. Thus all our patients who died with renal insufficiency had an active infection at autopsy and only one of our eighteen

living and presumably cured patients has evidence of renal damage attributable to bacterial endocarditis. In addition, seven of our thirty-nine adequately treated patients showed transient evidence of renal damage which cleared while they were on antibiotic therapy.

One of the unexpected features of this series, in view of the general opinion to the contrary, was the finding of congestive heart failure anteceding the onset of bacterial endocarditis in five cases and as the initial manifestation of bacterial endocarditis in eight cases. A severely damaged valve may, of course, cause congestive heart failure without the insult of the bacterial endocarditis; but the patient may be in a borderline state of compensation and the added burden of a low-grade fever, anemia or increased valvular deformity may be enough to precipitate congestive heart failure early in the course of bacterial endocarditis. That the appearance of congestive heart failure in bacterial endocarditis is at least in part determined by the degree of pre-existing valvular deformity is supported by the absence of any significant difference in the time between onset of the disease and adequate therapy or death in the twenty-one patients who developed congestive heart failure, as compared to the eighteen patients who never developed congestive heart failure.

Another factor which seems to have some importance in determining the appearance of congestive heart failure is the valve involved by the infection.[18,21,23,30] Thus in our cases, when the aortic valve alone was involved with bacterial endocarditis, the chances of developing congestive heart failure appeared to be greater than when the mitral valve alone was involved. Our figures on this aspect are not too satisfactory since we were dealing with an almost exclusively male population and the incidence of aortic valvular involvement with rheumatic heart disease is greater in males than in females.

The presence of congestive heart failure does not seem to affect the cure rate of bacterial endocarditis since the cure rate in the twenty-three adequately treated patients with congestive heart failure was 65 per cent, which compares favorably with the 69 per cent cure rate for the group as a whole. On the other hand, as others have reported,[1,6,23,25] the mortality rate in adequately treated patients with congestive heart failure is much higher than in those patients without congestive heart failure. In our series this mortality rate was 74 per cent, which compares unfavorably with 54 per cent for the group as a whole. Another important feature of the thirteen patients with antecedent congestive heart failure or congestive heart failure as an initial manifestation of bacterial endocarditis is that eight of these patients were inadequetely treated or were untreated. We wish, therefore, to stress again the importance of maintaining a high degree of suspicion for bacterial endocarditis even in the presence of congestive heart failure.

Of practical value and of great interest is the observation in our series that when a positive blood culture was obtained it appeared in at least one of the first four cultures taken. On the basis of this observation we have limited to four the number of blood cultures taken in suspected cases of bacterial endocarditis.

A vivid illustration of the indolent nature that this disease may assume was afforded by the discovery of positive blood cultures in three patients who were afebrile.

Contrary to other reports,[21] we found no effect from inadequate sporadic antibiotic therapy on our success in obtaining positive blood cultures and we have also been able to obtain positive blood cultures from individuals whom we thought were receiving adequate antibiotic therapy but were not doing well clinically.

SUMMARY AND CONCLUSIONS

1. Fifty-two cases of proven bacterial endocarditis collected in a six and one-half year period from the Bronx Veterans Administration Hospital are analyzed.

2. The need for new diagnostic and therapeutic criteria for bacterial endocarditis is indicated.

3. The effect of duration of disease and of inadequate sporadic antibiotic therapy on the eventual curability of bacterial endocarditis in this group is discussed.

4. Bacteriologic cure of bacterial endocarditis seemed to have a beneficial effect on the renal lesions capable of causing renal insufficiency in this group of cases.

5. Congestive heart failure and auricular fibrillation occurred early in the course of bacterial endocarditis in 25 per cent and 15 per cent of our patients. These, therefore, should not be considered rare findings in this disease.

6. An important factor in the appearance of congestive heart failure during bacterial endo-

carditis would seem to be the degree of preexisting valvular deformity.

7. Congestive heart failure had no effect on bacteriologic cure rate in our cases of bacterial endocarditis but had an adverse effect on the mortality rate in adequately treated patients. The mortality rate in this group was 74 per cent.

8. Positive blood cultures may be obtained from afebrile patients.

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The Mechanism of Formation of Left Auricular Mural Thrombi*

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EMBOLIZATION is responsible for death in more than 20 per cent of patients who die of rheumatic heart disease.[1a] In an additional number emboli may cause serious and permanent disability. These figures will probably increase with increasing prophylactic and therapeutic control of the other complications of rheumatic heart disease such as bacterial endocarditis and cardiac failure due to valvular stenosis.

Further study of those patients who are liable to the risk of embolization may provide additional opportunity to diminish the mortality and morbidity of rheumatic heart disease. The incidence and location of mural thrombi, the source of emboli, and the occurrence of occlusive auricular thrombi in patients with rheumatic heart disease have been reported previously.[1] The present study is concerned with the factors responsible for the formation and development of thrombi in the chambers of the heart in these patients.

The frequent association of auricular mural thrombi with severe mitral stenosis has often been noted. This association is particularly common in the presence of auricular fibrillation[2–4] and in the older age groups, i.e., over forty years.[4] Some authors have considered heart failure to be an additional significant factor.[6] These conditions are said to increase the frequency of auricular mural thrombi by producing "stasis" in the auricle.[2,5,6]

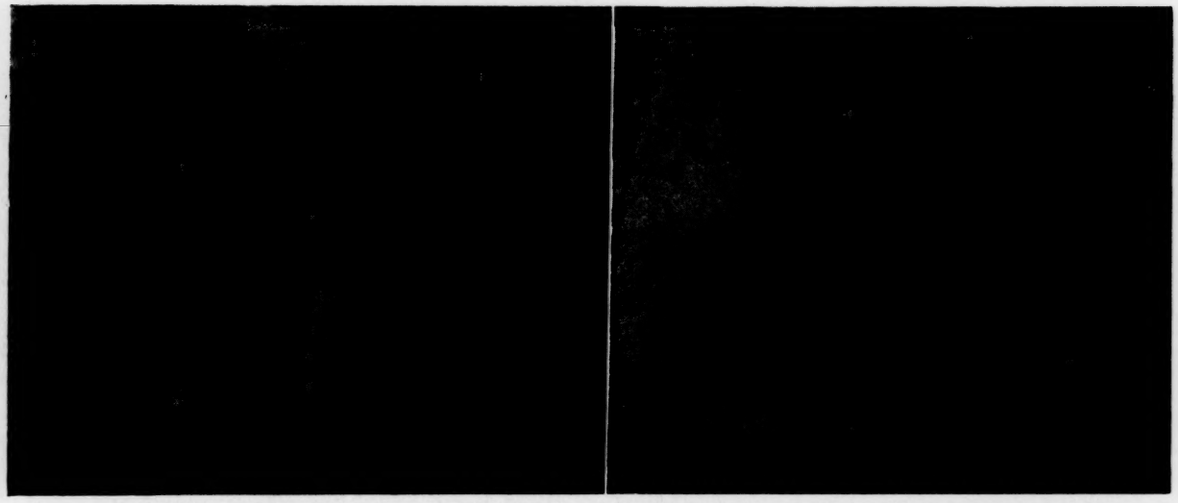
MATERIAL

In order to study some of the factors responsible for the formation of atrial mural thrombi 8,676 consecutive cases examined postmortem at the Queens General Hospital from 1936 to 1950, inclusive, were reviewed. Of these 509 (5.9 per cent) were considered to be instances of rheumatic heart disease and were selected according to criteria previously described.[1b] Seventy-two with minimal rheumatic involvement and 103 examples of calcific aortic stenosis were excluded. Thrombi were found within the cardiac chambers in 137 instances (26.9 per cent). All of these cases were analyzed and form the basis of the present study. In addition, many more recent cases were studied in view of the ideas presented below but have not been included in the figures cited.

FACTORS IN THE FORMATION OF AURICULAR MURAL THROMBI

Altered Dynamics Due to Valvular Changes. The presence of mitral insufficiency with stenosis allows the regurgitation of a relatively narrow stream of blood which strikes the same small area of the auricular wall with each ventricular contraction. This regurgitant jet of blood is familiar to surgeons at the time mitral commissurotomy is being performed.[7] Over a period of many years impingement of the regurgitant jet upon the auricular wall leads to collagenous thickening of the endocardium at that site. (Fig. 1.) Devitalization of such auricular endocardium by any of several mechanisms, including physical trauma and other injuries most of which remain unknown, favors the formation of non-bacterial thrombotic endocarditis at this site. (Fig. 2.) This is analogous to the explanation for the location of non-bacterial thrombotic endocarditis on the valve where repeated trauma and similar collagenous thickening accounts for the predilection for this site.[8,9] It is presumed that this non-bacterial thrombotic nidus offers a starting point for the deposition of the mural thrombus (Fig. 3) as it does for the valvular vegetation. In recently studied cases of rheumatic heart disease with thrombi in the left auricle a probe has been passed through the mitral orifice from the ventricle into the auricle to correspond to

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1 2

FIG. 1. View of the dilated left atrium and stenotic mitral orifice from the superior aspect of the left auricle. Probe entering the left atrium through a slit-like mitral orifice, corresponding to the regurgitant stream of blood, impinges on the area of thickened puckered endocardium indicated by two arrows.

FIG. 2. View of the left atrium and the previously opened stenotic mitral orifice below, as seen from the lateral aspect. Probe entering the left atrium through the mitral orifice, corresponding to the regurgitant stream of blood, impinges on a lesion of non-bacterial thrombotic endocarditis (arrow 1); this is superimposed upon an area of thickened endocardium. Arrow 2 indicates another non-bacterial thrombotic lesion on the valve edge.

the refluxed stream of blood. The probe strikes the auricle wall in the center of the mural thrombus or in the most built-up portion of the clot. (Fig. 3.) In larger or older clots it may be difficult or impossible to identify histologically the underlying non-bacterial thrombotic lesion, particularly when organization of the base has occurred. In some rheumatic hearts without mural thrombi the probe has impinged on the auricular wall at the site of a non-bacterial thrombotic vegetation. (Fig. 2.) Although this mechanism represents the most common manner in which atrial thrombi are initiated, some instances represent gradual extension of thrombus from the auricular appendage. (Fig. 4.)

In rheumatic hearts mural thrombi occur more frequently in the left than in the right auricle[11] for two reasons. Stenosis and insufficiency of the mitral valve are much more common and more severe than of the tricuspid valve. The force imparted to the regurgitant stream of blood is greater because the systolic pressure in the left ventricle considerably exceeds that in the right ventricle. The significance of this factor of intracardiac pressure has been illustrated previously by the increased frequency of mural thrombi in the left auricle and appendage, when severe mitral stenosis is associated with severe aortic involvement, compared to those cases with severe involvement of the mitral valve alone.[1b]

In the presence of mitral stenosis and insufficiency mural thrombi are not as likely to form on the ventricular endocardium as on the auricular endocardium. This may be accounted for by comparing the relative force imparted to the stream of blood by the contraction of each chamber since ventricular systolic pressure is so much greater than auricular pressure.

Mitral regurgitation alone or in association with minimal stenosis would be expected to give a lower incidence of mural thrombi since the regurgitant stream of blood strikes the auricle wall more diffusely and possibly with less force.

Another factor is the occurrence of this condition over a long period of time, that is many years. It is probable that the greater incidence of auricular mural thrombi noted with increased age and with the presence of auricular fibrillation[2,4] is only a reflection of the longer duration of the disease during which the altered hemodynamics may produce the local changes described.

The variable degree of combined functional mitral insufficiency and stenosis present from case to case, and the unpredictable conditions which alter the collagen of the atrial wall[9] are the chief factors which determine whether or not

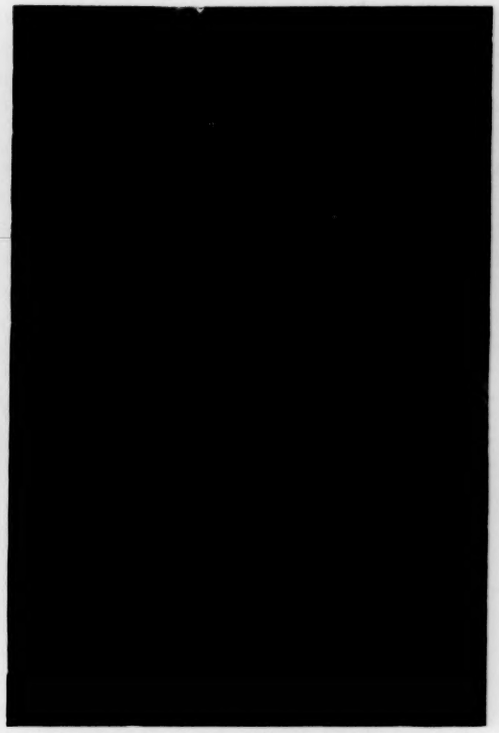


FIG. 3. Lateral view of the left atrium, previously opened stenotic mitral orifice, and chamber of the left ventricle. Probes entering the atrium delineate the large mural thrombus. In a thrombus of this size it is usually impossible to identify the underlying non-bacterial thrombotic lesion histologically because of its relatively small size and incorporation within the thrombus. The arrow indicates a separate thrombus in the left auricular appendage.



FIG. 4. View of the opened left auricular appendage and adjacent atrial wall above stenotic mitral valve. Upper arrow shows the atrial mural thrombus which has extended from the thrombus in the left appendage. The lower arrow indicates a non-bacterial thrombic lesion on the valve edge.

mural thrombi will occur in the left auricle. Until these functional variations can be estimated clinically in conjunction with the other factors to be described, it would be rather difficult to predict in any individual case whether or not mural thrombi have developed or will develop unless incidental collateral evidence is available in the form of systemic emboli.

Role of Auricular Fibrillation. There is an increased frequency of auricular mural thrombi when auricular fibrillation is present.[2–4] It is probable that several mechanisms play a role. One of these may be the effect of auricular fibrillation on the ventricular rate, since with an increased ventricular rate the regurgitant stream of blood impinges on the auricular wall that many more times per minute. Auricular fibrillation may also increase the effect of the regurgitation by preventing contraction of the auricular wall, thereby allowing the position of the auricular endocardium to remain constant in relation to the time of ventricular systole and thus continuously exposing the same relatively small area to the impinging regurgitant stream of blood. Even in the presence of a slow ventricular rate, auricular fibrillation would produce variability in the strength of ventricular contraction with increased frequency in the number of systoles of greater than normal force. Dilatation of the ventricle may produce relative mitral regurgitation in cases in which this was prevented during systole by impingement of the ventricular wall against a laterally directed mitral orifice. (Fig. 5, Group A.)[10]

Since it is difficult to conceive of blood remaining static on the vertical smooth auricular wall even in the presence of auricular fibrillation, the mechanism of "stasis" to explain the increased frequency of mural thrombi in the auricle in the presence of auricular fibrillation would seem rather inadequate. Furthermore, "stasis" would not account for the location of these thrombi high up on the posterior wall. The concept of stasis also overemphasizes the significance of auricular systole in emptying these chambers which normally play a largely passive role as temporary reservoirs until the auriculoventricular valves reopen. The only real opportunity for stasis to occur would seem to be in the auricular appendage where blood might accumulate between the trabeculae. However, the failure to

demonstrate a significantly greater frequency of thrombi in the appendage as compared with the auricle[1b] seems to make this consideration of less significance. Although considerable stasis occurs in the left ventricle during cardiac failure, mural thrombi in the ventricles are rare in the absence of underlying myocardial infarction. Similarly mural thrombi in aortic aneurysms are secondary to underlying changes in the endothelium rather than to stasis. "Stasis" resulting from auricular fibrillation also fails to account for the much greater frequency of thrombi in the left compared to the right atrium in cases of rheumatic heart disease, and the converse finding in non-rheumatic hearts;[11] this emphasizes the importance of the valvular lesion in producing a regurgitant stream of blood.

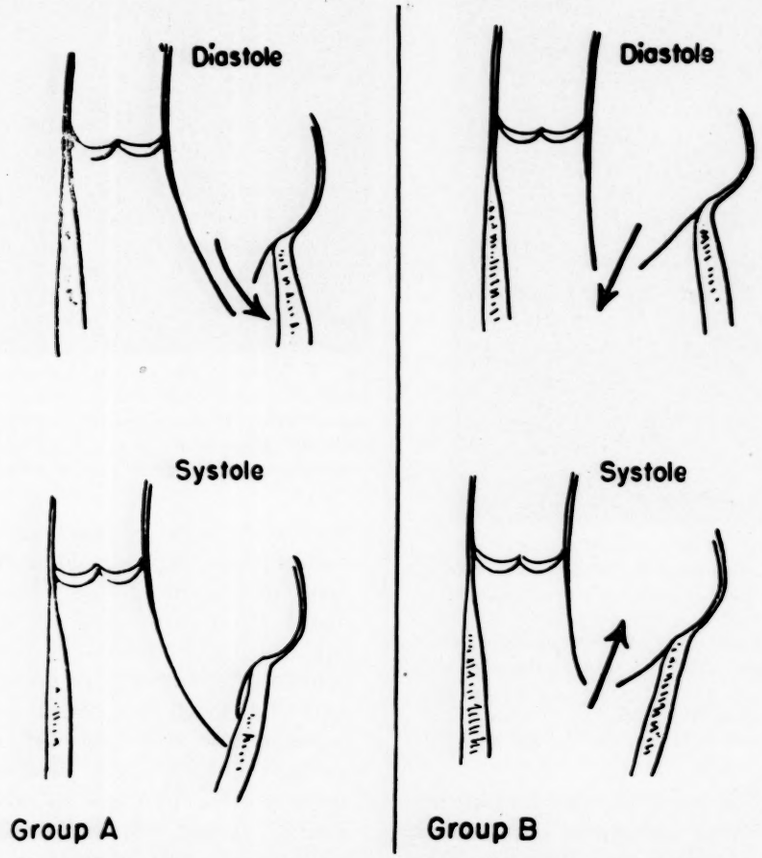


FIG. 5. Diagram of left auricle and ventricle indicates how the ventricle may impinge against a laterally directed mitral orifice during systole (Group A) and thereby prevent mitral regurgitation. (From Harken et al. *Circulation*, 5: 349, 1952.)

Altered Clotting Mechanisms. An additional significant factor necessary to account for the development of mural thrombi over a period of many years would seem to be some transitory alteration in the clotting mechanism of the blood, presumably independent of the previously described processes. These alterations in the clotting mechanism may occur as a result of drugs, relatively minor or major intercurrent unrelated illnesses, variations in dietary intake and fluid balance and many other factors which have, as yet, been inadequately studied. It is quite conceivable that such transitory variations in clotting mechanisms occur frequently in all normal people; however, in rheumatic patients who have the predisposing factors described, a nidus for the deposition of thrombus is available. When the alteration in clotting mechanisms is combined with this readily available site, mural thrombosis is initiated.

Role of Subacute Bacterial Endocarditis. The rarity of mural thrombi in the auricle in association with subacute bacterial endocarditis has

been noted previously.[2] It is possible that this is due to the adverse effect that subacute bacterial endocarditis has on the longevity of the patient. The clinical observation that auricular fibrillation and subacute bacterial endocarditis infrequently accompany each other[12,13] may further account for the rarity of mural thrombi in subacute bacterial endocarditis.

Role of Auricular Infarction and Active Rheumatic Auricular Endocarditis. True auricular infarction is almost always associated with an overlying mural thrombus. Auricular infarction is a rare phenomenon, however, and it is likely that degeneration or death of auricular muscle fibers occurs more often because of an overlying thrombus than the reverse sequence. The auricular tissue is far more dependent upon nutrition received from blood within the lumen of the chamber itself than is the ventricular musculature. In patients who have had auricular mural thrombi for any length of time and show associated alteration in the auricular muscle, it may be impossible to tell merely from the histologic appearance which was the initial phenomenon. However, since auricular infarction occurs almost exclusively in the right auricle,[11] this does not offer an adequate explanation for the development of left auricular mural thrombi.

Graef and his co-workers[14] considered persistence of active auricular endocarditis to be one of the chief factors in the production of auricular thrombi. However, the pathologic criteria in their study included cases in which Aschoff bodies were not found and some of the histologic changes described may be secondary to the overlying thrombi. Furthermore, this mechanism fails to explain the absence of mural thrombi over areas of rheumatic activity in the ventricle, as well as the low incidence of thrombi in younger patients in whom rheumatic activity is most diffuse and most intense. In their study Weiss and Davis[3] concluded that the presence of rheumatic activity was not a factor in the formation of auricular thrombi. Recent workers[11,15] have also presented findings which minimize the significance of rheumatic activity in the formation of auricular thrombi.

SUMMARY AND CONCLUSIONS

The significant factors associated with formation of thrombi in the left atrium were studied in 509 consecutive autopsied cases of rheumatic heart disease. These factors include valvular distortion, non-bacterial thrombotic endocarditis, age of the patient and duration of the disease, auricular fibrillation, alterations in the clotting mechanism, subacute bacterial endocarditis, auricular infarction and rheumatic activity. The manner in which each contributes to the formation of mural thrombi in the atrium is discussed.

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Effects of Vigorous Physical Exercise on Cerebral Circulation and Metabolism*

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THE relative importance of carbon dioxide content and tension and arterial blood pH levels in the regulation of cerebral vascular tone has not been completely settled. Kety and Schmidt have demonstrated the direct relationship between arterial carbon dioxide tension and cerebral blood flow and the inverse relationship between arterial blood pH and cerebral blood flow during inhalation of 5 to 7 per cent carbon dioxide or hyperventilation.[1,2] Patterson, Heyman, and Duke showed that in emphysematous patients there was a rough direct relationship between arterial carbon dioxide tension and cerebral blood flow,[3] though recent studies in patients with less severe emphysema have failed to confirm this relationship.[4] The studies on diabetic coma by Kety et al.[5] served to separate partially the two factors of hydrogen ion concentration and carbon dioxide tension of the blood by demonstrating cerebral vasodilatation in the presence of a markedly decreased arterial carbon dioxide tension with increased blood hydrogen ion concentration. On the other hand, Schieve and Wilson have demonstrated that metabolic alkalosis, produced by 3 per cent $NaHCO_3$, results in increased cerebral blood flow, and metabolic acidosis, produced by 0.8 per cent NH_4Cl, results in decreased cerebral blood flow.[6] These authors conclude that cerebral vascular tone is more closely related to arterial CO_2 content than to arterial blood pH. Their observations on carbon dioxide tension were incomplete.

The present study was undertaken in an effort to learn more about the effects of changes in arterial blood pH and carbon dioxide content on cerebral vessels, for vigorous physical exercise by untrained subjects is known to result in decreased arterial blood carbon dioxide content and pH with only small and variable alterations in arterial carbon dioxide tension.[7] Since exercise also results in other circulatory and biochemical changes, these studies, like those previously mentioned on diabetic acidosis and pulmonary emphysema, do not measure strictly the effects of alterations in blood pH and carbon dioxide content or tension on cerebral circulation. Another purpose of the study was to gather information concerning the effects of exercise, whatever they might be, on cerebral hemodynamics and metabolism.

METHOD

Included in this study were twelve normal, untrained young men, ranging in age from eighteen to thirty-eight years and one normal woman, age twenty-seven. The subjects were all students at the University of Miami. They came to the laboratory fasting and without smoking. The initial cerebral blood flow procedure was carried out in the usual manner with the subject supine.[8] After a twenty-minute rest period the subjects began walking on a non-automatic treadmill with their needles still in place. The subjects walked at a rapid pace on a 4.0 per cent grade; and although no effort was made to measure work performed, the exercise was severe and vigorous for all subjects. Rough calculations revealed that the subjects walked at an average of 4.5 miles per hour for forty minutes. After the subject had exercised for eighteen to twenty minutes, initial blood samples for pH, carbon dioxide and oxygen content, oxygen saturation, and glucose content were drawn, and immediately thereafter the cerebral blood flow was measured. The nitrous oxide mixture

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was delivered by a valve permitting flows as high as 150 to 200 L. per minute to accommodate the increased respiratory demands of the subjects. Those subjects who had a striking drop in arterial pressure in the upright position, or who complained of faintness, were eliminated from the study. Blood samples for oxygen and glucose were again drawn immediately at the end of the blood flow measurement while the patient was still exercising. The average of the two A-V O_2 and A-V glucose difference obtained before and after each flow is used as the result in each instance. The carbon dioxide contents, blood pHs and respiratory quotients used in analyzing the results were those that were measured just before the cerebral blood flow measurement was begun in both the control and exercise portions of the study.

Arterial pressure was measured by auscultation with arm held at heart level every minute during the flow procedures. Average mean pressures were calculated by adding one-third of the pulse pressure to the diastolic pressure. The mean cerebral arterial pressure in the erect position during exercise was calculated by subtracting from the mean erect brachial arterial pressure the vertical distance in mm. Hg from the second rib to the mid-cerebrum.

The blood samples were analyzed for nitrous oxide and calculations for cerebral blood flow and the other cerebral vascular and metabolic functions were calculated in the usual way.[8] Blood oxygen content and per cent oxygen saturation were determined by a spectrophotometric method.[9] Arterial and venous oxygen tensions were estimated from the per cent saturation and pH using the dissociation curves of Dill. Since it is not possible to read these curves accurately when oxygen saturation is above 90 per cent, tables of calculated values were used under those circumstances, and it is emphasized that the results given are estimates of arterial oxygen tension. The pH of whole blood was measured with a Cambridge Model R pH meter with an inclosed glass electrode. Measurements were made at 33 to 34°C. immediately after the samples were drawn and corrected to 38°C. by Rosenthal's factor.[10]

The carbon dioxide content of whole blood was measured by the method of Van Slyke and Neill[11] and carbon dioxide tension was calculated by the nomograms of Peters and Van Slyke.[11] Blood glucose content was measured by the sodium thiosulfate titration technic of Somogyi.[12]

TABLE I

Pt.	Arterial O_2 Content (vol. %)		Venous O_2 Content (vol. %)		Arterial O_2 Tension (mm. Hg)		Venous O_2 Tension (mm. Hg)		Arterial O_2 Saturation (%)		Arterial CO_2 Content (vol. %)		Venous CO_2 Content (vol. %)		Arterial pH		Venous pH		Arterial CO_2 Tension (mm. Hg)		Venous CO_2 Tension (mm. Hg)	
	C.	E.	C.	E.	C.	E.	C.	E.	C.	E.	C.	E.	C.	E.	C.	E.	C.	E.	C.	E.	C.	E.
T. N.	18.9	19.2	13.2	12.8	110	106	38	38	98	97	47.8	41.6	52.9	48.9	7.37	7.34	7.33	7.31	42	41	51	50
R. F.	17.1	16.9	9.8	8.6	91	103	33	31	96	96	48.5	42.8	56.4	51.2	7.33	7.29	7.27	7.26	46	45	61	56
S. B.	20.6	22.0	13.2	14.0	95	103	37	37	96	96	44.0	38.6	50.4	45.2	7.35	7.28	7.28	7.25	41	43	53	51
M. R.	18.6	20.2	11.1	11.4	97	111	34	33	96	97	46.6	38.5	54.1	46.9	7.34	7.29	7.27	7.24	44	40	59	55
L. T.	18.9	20.7	13.4	14.2	86	115	40	41	95	97	44.9	40.0	49.6	46.3	7.34	7.29	7.30	7.24	43	43	50	55
M. C.	19.2	20.2	11.5	11.5	96	97	35	33	96	96	49.4	45.4	56.5	52.9	7.35	7.31	7.27	7.27	46	46	61	58
W. W.	17.4	18.7	10.9	10.7	83	111	34	33	95	97	46.9	41.6	53.8	48.4	7.36	7.24	7.32	7.18	42	47	58	65
J. M.	20.9	21.3	14.6	15.3	112	98	40	42	99	96	47.3	41.5	53.0	47.5	7.37	7.29	7.32	7.26	42	45	52	56
E. P.	21.6	21.8	14.7	14.8	115	114	41	41	98	97	47.4	44.6	53.8	51.7	7.35	7.28	7.28	7.24	44	48	57	60
A. L.	19.4	21.0	14.3	13.3	75	90	41	37	94	95	48.7	44.0	51.3	51.4	7.38	7.29	7.30	7.24	42	46	52	60
A. G.	18.5	19.8	11.8	12.5	99	112	37	39	97	97	45.4	41.3	51.4	48.1	7.35	7.28	7.28	7.22	42	45	55	60
L. D.	15.2	17.3	9.4	7.8	86	120	36	33	95	97	50.3	37.2	56.0	46.6	7.36	7.25	7.26	7.14	45	45	63	68
W. C.	18.4	19.4	11.9	11.8	81	86	35	34	94	95	46.9	42.4	53.6	49.0	7.35	7.31	7.30	7.28	43	43	55	52
Mean	18.8	19.9	12.3	12.2	94	105	37.0	36.3	96.1	96.4	47.2	41.6	53.3	48.8	7.35	7.29	7.29	7.24	43.2	44.4	55.9	57.4
p Values for change	<0.01		.....		0.01		.....		.....		<0.01		<0.01		<0.01		<0.01		>0.1		.....	

C = Control
E = Exercise

RESULTS

The results are given in detail in Tables I and II. Interpretation of the data must be tempered

by the fact that the exercise was performed in the upright position whereas the control observations were made with the subjects supine. The changes in cerebral blood flow and metabolism which occur in the upright position during motionless standing have previously been measured,[8] so that the effects of exercise must be analyzed by first considering the changes which would have occurred simply by having the subjects stand upright without exercising.

gest that exercise prevents this decrease in mean cerebral blood flow. There was a consistent increase in arterial-cerebral venous oxygen difference (A-VO_2), averaging 19 per cent, during exercise. This change is almost identical (23 per cent) to that which occurs in motionless standing.

TABLE II

Pt.	Age	Cerebral Blood Flow (ml./min./100 gm. brain)		Arterial Cerebral Venous O_2 Difference (vol. %)		Cerebral O_2 Consumption (ml. O_2/min./100 gm. brain)		R. Q.		Arterial Cerebral Venous Glucose Difference (mg. %)		Cerebral Glucose Consumption (mg. glucose/min./100 gm. brain)		A-V Glucose / A-V O_2		Mean Arterial Pressure (mm. Hg)		Cerebral Vascular Resistance (mm. Hg./ml. blood/100 gm. brain/min.)	
		C.	E.	C.	E.	C.	E.	C.	E.	C.	E.	C.	E.	C.	E.	C.	E.	C.	E.
T. N.	32	107	86	5.7	6.4	6.1	5.5	0.94	0.97	7.7	6.5	8.2	5.6	1.35	1.02	82	47	0.77	0.55
R. F.	31	51	85	7.4	8.2	3.8	7.0	1.01	1.02	8.5	9.4	4.3	8.0	1.15	1.15	95	64	1.85	0.75
S. B.	26	72	76	7.3	8.0	5.3	6.1	0.93	0.93	10.1	10.6	7.3	8.1	1.38	1.33	100	71	1.39	0.94
M. R.	37	61	49	7.5	8.9	4.6	4.3	0.99	0.94	11.7	8.5	7.2	4.3	1.56	0.96	94	65	1.54	1.32
L. T.	19	72	56	5.5	6.5	4.0	3.6	0.90	0.97	6.4	9.4	4.6	5.3	1.16	1.45	80	52	1.11	1.07
M. C.	18	56	68	7.7	8.7	4.3	5.9	0.89	0.86	10.5	12.0	5.9	8.2	1.37	1.38	83	56	1.48	0.82
W. W.	33	46	48	6.5	8.1	3.0	3.9	1.03	0.90	8.2	11.7	3.8	5.6	1.26	1.44	76	55	1.65	1.05
J. M.	19	42	80	6.3	6.0	2.7	4.8	0.90	1.00	10.0	9.8	4.3	7.8	1.59	1.63	77	54	1.72	0.60
E. P.	20	44	43	6.9	7.0	3.0	3.0	0.93	0.96	9.8	6.2	4.3	2.7	1.42	0.89	98	80	2.23	1.88
A. L.	23	32	52	5.2	7.7	1.7	4.0	0.97	0.96	7.4	13.3	2.4	6.6	1.42	1.73	90	87	2.81	1.67
A. G.	22	38	47	6.7	7.3	2.5	3.4	0.90	0.89	7.4	10.9	2.8	5.1	1.10	1.49	73	46	1.92	0.98
L. D.	27	67	58	5.8	9.5	3.9	5.5	1.02	0.99	8.7	11.6	5.8	6.7	1.50	1.22	81	70	1.21	1.21
W. C.	38	64	45	6.6	7.6	4.2	3.4	1.02	0.97	10.7	7.7	6.8	3.5	1.62	1.01	84	62	1.31	1.38
Mean		57.9	61.0	6.5	7.7	3.78	4.65	0.95	0.94	9.01	9.82	5.21	5.96	1.38	1.28	85.6	61.2	1.61	1.08
p Values for change		>0.5		<0.01		>0.02, <0.05		.....		.....		.....		.....		<0.01		<0.01	

C = Control
E = Exercise

Changes in cerebral blood flow (CBF) during exercise were variable, and this variability could not be attributed to any known factor measured in this study or to the subjective reaction of the subject. As contrasted with the consistent fall in cerebral blood flow, averaging 21 per cent, observed in motionless standing, these data suggest that exercise prevents this decrease in mean cerebral blood flow. There was a consistent increase in arterial-cerebral venous oxygen difference (A-VO_2), averaging 19 per cent, during exercise. This change is almost identical (23 per cent) to that which occurs in motionless standing.

Cerebral oxygen consumption ($CMRO_2$) increased during exercise from a mean of 3.78 to 4.65 ml. O_2/min./100 gm. brain. This increase appears to be statistically significant, particularly when contrasted to the lack of change resulting from motionless standing. Since the A-V O_2 used in the results was the average of oxygen samples drawn before and after exercise, it was believed that the increased $CMRO_2$ may have been related to a gradual increase in A-V O_2 during exercise, reflecting

an actual decrease in CBF similar to that which occurs in motionless standing. This may occur because the nitrous oxide method measures only the mean CBF over the ten-minute period of gas inhalation; and if CBF fell rapidly during the last two to four minutes of the testing period, this fall would not be accurately recorded. Further inspection revealed, however, that A-V O_2 differences drawn before and after the exercise blood flow were almost identical in practically every instance, indicating that the effects of exercise on A-V O_2 and probably CBF had become stabilized after the initial eighteen to twenty minutes of exercise and did not change significantly during the ensuing ten minutes of exercise.

Arterial-cerebral venous glucose difference (A-V gl) and cerebral glucose consumption (CMR gl) did not change significantly during exercise, although there was a tendency for both to increase, whereas there was a tendency for CMR gl to decrease during motionless standing. There was no significant alteration in arterial glucose level during exercise, an observation which has been made by others. Methods for measuring blood glucose content are probably not sufficiently accurate or reproducible to detect small changes in glucose metabolism. There was no significant change in the A-V glucose/A-V O_2 ratio or respiratory quotient (R.Q.).

Mean cerebral arterial pressure decreased 29 per cent during exercise, but the majority of this decrease was related to the increased vertical distance from the heart to the mid-cerebrum resulting from assuming the upright posture. Systolic pressure increased and diastolic decreased in every individual, but exercise apparently had little effect on mean pressure, for a 34 per cent decrease in mean cerebral arterial pressure resulted from motionless standing. Mean cerebral vascular resistance decreased 33 per cent, approximately twice as great as the decrease resulting from motionless standing. This is a statistically significant change and is probably a reflection of the degree of cerebral vasodilatation which occurs during exercise in the upright posture. (Table III.)

There was a small but consistent increase in arterial oxygen content and capacity, within the range previously reported by others,[7] but no alteration of per cent oxygen saturation. Calculated arterial oxygen tension actually showed a slight increase during exercise, contrary to results of other observers,[13] but our methods for measuring this value were not sufficiently accurate to justify further comment. There was no change in cerebral venous oxygen tension, suggesting that the increased cerebral oxygen extraction (A-V O_2) during exercise may have resulted partially from the increased oxygen available in the arterial blood.

TABLE III
CHANGES IN CEREBRAL VASCULAR AND METABOLIC FUNCTIONS DURING EXERCISE IN THE UPRIGHT POSITION AS COMPARED TO THE CHANGES RESULTING FROM MOTIONLESS STANDING

	Standing (%)	Exercise (%)
CBF	−21	0
A-V O_2	+23	+19
$CMRO_2$	0	+24
MAP	−34	−29
CVR	−16	−33

There was a consistent and considerable decrease of pH and CO_2 content in both arterial and cerebral venous blood during exercise, with no significant alteration in arterial or venous CO_2 tension. There was no further change in CO_2 content or pH after the first eighteen to twenty minutes of exercise, as indicated by samples drawn ten to twelve minutes later. The decreased pH and CO_2 content reflects the increase in blood lactic acid during exercise[14] and is an indication of the severity of the exercise.

COMMENTS

The significance of the fall in cerebral vascular resistance during exercise in the upright posture cannot be adequately interpreted on the basis of available data, a similar problem to that which arose in interpreting the data on motionless standing.[8] The decrease in cerebral vascular resistance may be due entirely to dilatation of cerebral vessels or partially to a decrease in pressure on the venous side of the cerebral capillaries, since pressure in the internal jugular system must certainly decrease in the upright position. Adequate internal jugular pressure measurements in man under these circumstances are not available so that no quantitative estimate of the effect of this alteration in dynamics can be given. Many factors would influence such a measurement, including the tendency of the vein to collapse when zero or negative pressures are

reached and the possible presence of one or more valves in the caudal portion of the internal jugular system. Despite these qualifications it can be reasoned that exercise must have resulted in some cerebral vasodilatation. The decrease in cerebral vascular resistance during exercise is about twice as great as that resulting from motionless standing whereas the decrease in mean arterial pressure was about the same in both experiments; judging from measurements of right atrial and superior vena cava pressures during exercise, there is no reason to believe that exercise produced a greater drop in jugular venous pressure than does motionless standing.

The data presented here cannot be compared with those of Kleinerman and Sokoloff[15] for the exercise was much more severe in our studies. The cerebral vasodilatation resulting from exercise is difficult to explain adequately but at least offers additional convincing evidence that the cerebral vessels may dilate in the presence of a decrease in arterial CO_2 content, and that this dilatation may occur without any alteration in arterial CO_2 tension. Exercise, then, is somewhat analogous to diabetic acidosis in the sense that both represent a variety of organic acidosis, resulting in the former from accumulation of lactic acid and in the latter from ketone bodies. In both instances cerebral vasodilatation seems to occur in the presence of increased hydrogen ion concentration, but in the exercise studies there is no correlation between alterations in pH and CVR or between pH and CBF or between pH and $CMRO_2$. Nor can any correlation be made out between arterial or venous carbon dioxide content or tension and any of the cerebral vascular or metabolic functions.

Likewise the increase in $CMRO_2$ is difficult to explain. The increase in metabolic rate of the body as a whole which occurs in exercise would seem to be a reflection of the increased metabolism of those organs primarily participating in the exercise, mainly the muscles. In what manner exercise results in increased metabolism of brain cells is not known. The only measured function which correlates statistically with $CMRO_2$ is CVR (Fig. 1), with a p value < 0.01, and the significance of this correlation cannot be explained by the available data. Studies in myxedema indicated that cerebral metabolic requirements may serve to regulate cerebral vascular tone[16] but it is not known if the increased metabolic demands of the brain in exercise resulted in decreased cerebral vascular tone, or whether the apparent correlation between these two functions is simply fortuitous. There is no reason to suspect that increasing the oxygen content of the arterial blood would result in increased $CMRO_2$, for previous studies have indicated that this does not occur.[1]

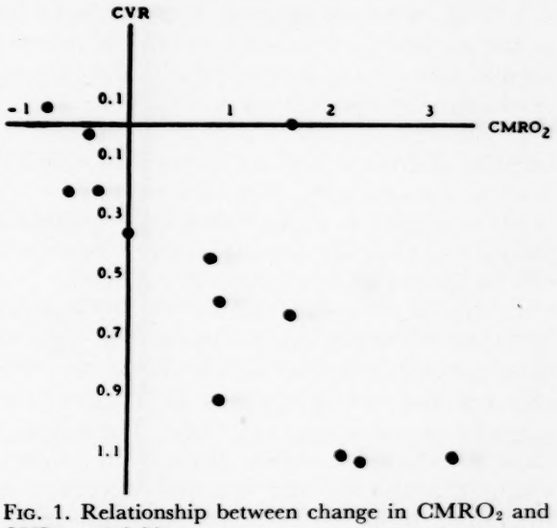


FIG. 1. Relationship between change in $CMRO_2$ and CVR. $p < 0.01$.

It is regrettable that determinations for blood lactic acid were not included in this study, for it would seem reasonable to anticipate that an elevation of blood lactic acid might result in some qualitative alteration of cerebral metabolism. In this study the absence of alteration of cerebral respiratory quotient under circumstances which must have resulted in increased blood lactic acid content would seem to indicate that the usual cycles for utilization of glucose by brain cells are not significantly affected by increased quantities of lactic acid.

The fact that mean CBF did not decrease during exercise (as contrasted to the decrease which might have been expected from assuming the upright posture without exercising) and the decrease in CVR resulting from exercise may simply reflect the increased cardiac output which results from exercise in normal subjects.[17] It is difficult to understand why cerebral vessels should respond passively to an increased cardiac output under the influence of exercise and not to the increases in cardiac output which result from apprehension[8] or hyperthyroidism.[18]

Evidence is now accumulating that the chemical regulation of cerebral circulation is complicated and not entirely consistent. Cerebral vascular resistance may be decreased in the

presence of an increased or decreased blood CO_2 content, an increased or decreased blood pH, and an increased, decreased or unchanged arterial blood pCO_2.

SUMMARY

1. The effects of vigorous muscular exercise in the upright posture were studied in thirteen normal subjects and compared with the changes resulting from motionless standing.

2. Exercise resulted in a decrease in cerebral vascular resistance and an increase in cerebral oxygen consumption. The decrease in mean cerebral blood flow which results from motionless standing did not occur with exercise. There was no change in cerebral respiratory quotient.

3. Although exercise resulted in a striking fall in blood carbon dioxide content and pH, no correlations could be made between these changes and the alterations in cerebral circulatory or metabolic functions. There was a close correlation between changes in cerebral vascular resistance and cerebral oxygen consumption, though the reason for this is not known.

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Review

Polyps of the Colon and Rectum*

Their Incidence and Relationship to Carcinoma

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THE literature contains many reports emphasizing the value of routine proctosigmoidoscopy in the early recognition of polyps and emphasizing also the relationship of polyps to cancer; however, there are few adequate follow-up studies. This paper describes a study of 7,487 patients undergoing proctoscopic and x-ray survey as part of a routine gastrointestinal examination during the period January 1, 1947, to December 31, 1951; 401 patients were found to have polyps of the rectum or colon. In the period from January 1, 1952, to December 31, 1952, all the patients with polyps were requested to return for a follow-up examination; 83.5 per cent of them did so. The specific purposes of the study were (1) to analyze the data with reference to the incidence of polyps, age and sex of polyp patients, signs and symptoms, location, size and histopathology, (2) to determine the rate of recurrence or formation of new polyps. (3) to study the possible relationship of these lesions to carcinoma of the colon and (4) to observe the fate of polyps manifesting features of early malignant changes and treated by local excision.

In this analysis the term polyp designates a general gross descriptive term for any tumor, regardless of size and whether sessile or pedunculated, projecting into the lumen of the bowel. Polyps associated with ulcerative colitis, grossly carcinomatous lesions, familial polyposis and extensive diffuse papillomatosis are not included.

INCIDENCE OF POLYPS OF RECTUM AND COLON AND GENERAL CHARACTERISTICS

Incidence: Review of Literature. The incidence of polyps, as reported in the literature, varies in relation chiefly to the type of analysis: (1) survey by cancer detection centers, (2) routine proctoscopic examinations or (3) autopsy study. Sex and age also are important factors; polyps are more common among men and in older age groups. The experience of three large cancer detection centers of the United States in the diagnosis of polyps is recorded in Table I. The incidence is lowest in the series based on the examination of women and highest in an older age group of a mixed population. The incidence of rectal and colonic polyps in routine proctoscopic examinations varies from 1.8 per cent to 12 per cent. (Table II.) The reports of several authors representing a total of 55,876 patients examined indicate 3,880 with polyps, an incidence of 5.1 per cent. The frequency of polyps at autopsy varies apparently with the completeness of the study. (Table III.) Atwater and Bargen,[20] using a hand lens to inspect the bowel minutely, found polyps in 69 per cent of routine examinations.

TABLE I
INCIDENCE OF POLYPS OF RECTUM AND COLON IN CANCER DETECTION SURVEYS

Source	No. and Type of Subjects Examined	Incidence (%)
Women's and Children Hospital Cancer Prevention Clinic, Chicago[1]	3,450 non-symptomatic women	2.6
Cancer Detection Center, University of Minnesota[2]	3,364 symptom-free individuals 45 years of age or more	17.2
Strang-Prevention Clinics, Kips Bay-Yorkville Cancer Detection Center[3]	7,494 normal, healthy adults	6.4

Incidence: Present Study. Polyps of the rectum

* From the Frank Billings Medical Clinic, Department of Medicine, University of Chicago, Chicago, Ill. This investigation was supported in part by a research grant from The National Cancer Institute of The National Institutes of Health, United States Public Health Service.

and colon were found in 401 of the 7,487 patients; the figure 5.4 per cent is almost identical with the average reported in the literature (Table II); 372 (92.8 per cent) were diagnosed by proctoscopy; 14 (3.2 per cent) of these also were demonstrable at x-ray; 29 (7.2 per cent) were diagnosed by roentgen examination alone. Single polyps were present originally in 352 (87.8 per cent) of the 401 patients; more than one polyp was found initially in 49 or 12.2 per cent of the group.

TABLE II
INCIDENCE OF RECTAL POLYPS IN ROUTINE PROCTOSCOPIC EXAMINATIONS

Author	No. of Patients	Material	Incidence (%)
Browne[4]	1,000	Routine proctoscopies	3.2
Brust[5]	3,998	Private and charity patients	5.3
Buie[6]	910	No abnormal intestinal habits	8.2
Castro[7]	12,000	Routine proctology clinic	2.4
Colvert[8]	10,200 est.	Routine	2.3
Diamond[9]	5,980	Routine examination in mental institution	6.8
Hauch[10]	1,919	Asymptomatic	8.1
Greer[11]	747	Routine proctoscopies	2.9
Jackman[12]	1,000	Without symptoms; age 30 to 70 years	12.0
	1,000	With bleeding, abdominal cramps and change in bowel habits; age 30 to 70 years	12.0
Rossien[13]	550	Referred to G. I. Clinic	3.5
Scarborough[14]	10,000	Routine	4.6
Shallenberger[15]	3,500	Consecutive sigmoidoscopies	7.6
Steele[16]	1,500	Routine proctoscopies	5.2
Turell[17]	386	50 years or over with intestinal symptoms	6.9
	386	Under age of 45 years; asymptomatic	1.8
Wertheimer[18]	300	Symptomatic; 90% examined for hemorrhoids	3.7
Yater[19]	500	Asymptomatic patients	8.8
Total	55,876	Average	5.1

TABLE III
INCIDENCE OF POLYPOID LESIONS OF THE COLON AT ROUTINE AUTOPSY

Author	No. of Patients	Incidence (%)
*Atwater[20] (1949)	241	69.0
Feyrter[21] (1931)	1,800	21.4
Helwig[22] (1947)	1,460	9.5
Hino[23] (1942)	394	17.5
Lawrence[24] (1936)	7,000	2.6
Mayo[25] (1942)	100	16.0
Stewart[26] (1931)	1,815	4.2
Susman[27] (1932)	1,100	6.0
Swinton[28] (1947)	1,843	7.0

* Examined with a hand lens.

Age and Sex. The age of the 7,086 patients without polyps averaged forty-four years. (Table IV.) The average age of the polyp group was fifty-two years. This difference in age is emphasized further by the equal distribution of patients in the age groups thirty-one to forty, forty-one to fifty and fifty-one to sixty in the normal patients, whereas in the polyp group the number in the sixth decade is threefold greater than that of the fourth decade of life. There was no significant difference in age between males and females. In the normal group the sex ratio was approximately 1:1. In the polyp group there were 255 males and 146 females, a male predominance of 3.5:2; this figure is in agreement with those in other similar studies.

TABLE IV
INCIDENCE OF ADENOMA OF THE RECTUM AND COLON ACCORDING TO AGE AND SEX COMPARED TO THE DISTRIBUTION OF AGE AND SEX OF THE TOTAL GROUP

Age (Decades)	Non-polyp Patients			Per cent	Polyp Patients			Per cent
	Male	Female	Total		Male	Female	Total	
0–10	15	11	26	0.4	1	0	1	0.2
11–20	56	50	106	1.5	0	0	0	0.0
21–30	393	432	825	11.5	6	8	14	3.5
31–40	867	946	1,813	25.5	31	22	53	13.2
41–50	982	941	1,923	27.0	63	31	94	23.4
51–60	762	861	1,623	23.0	91	54	145	36.1
61–70	337	301	638	9.0	49	26	75	18.7
71–80	70	53	123	2.0	10	5	15	3.7
81–90	4	5	9	0.1	4	0	4	0.9
Totals	3,486	3,600	7,086	....	255	146	401	....
Mean Ages	44.4	44.0	44.2	....	52.6	51.1	51.8	....

Symptoms and Signs. Turell[17] observed polyps in 2 per cent of 386 asymptomatic patients under the age of forty-five as compared to a 7 per cent incidence among 386 patients age fifty years or more with intestinal symptoms; the varying results may be explained by the differences in the age distribution. A more appropriate comparison is the study by Jackman[12] who found no difference in the incidence of benign rectal polyps in 1,000 patients without symptoms compared to 1,000 patients with a history of rectal bleeding, abdominal cramps and change in bowel habits. Our findings were similar to those of Jackman in that there were at least as many symptoms and signs in the control group. (Table V.)

Location of Polyps. Although there are exceptions,[24,27] most authors agree that the majority

of polyps are found in the distal 25 cm. of the colon. The anatomic distribution of the 583 polyps found in the 401 patients of this study is indicated in Figure 1. Approximately 73 per cent were located at levels from 0 to 15 cm.

TABLE V
SYMPTOMS AND SIGNS IN PATIENTS WITH AND WITHOUT POLYPS

	Polyp Group (401)		Control Group (363)	
	No.	Incidence (%)	No.	Incidence (%)
Abdominal pain	99	24.9	228	62.8
Blood in feces	181	45.1	133	36.6
Change in bowel habits (constipation and diarrhea)	116	28.9	115	31.7

above the anus; 16 per cent from 15 to 25 cm.; 11 per cent were beyond the 25 cm. level.

Size. Data on the size of the polyps were available in 564 of the 585 polyps. (Table VI.) Sixty-eight per cent of them were less than 1 cm. in diameter; of these 16.7 per cent were less than 3 mm.

TABLE VI
SIZE OF POLYPS

Size	No. of Polyps	Per cent
<3 mm.	93	16.7
3–5 mm.	242	42.7
6–9 mm.	50	8.9
1–2 cm.	145	25.7
3–4 cm.	27	4.8
>4 cm.	7	1.2
Total	564	

Histologic Classification. Interpretation of the histologic appearance of polyps is admittedly difficult. The microscopic diagnosis based on histology alone often will exaggerate potential malignancy. As a result of rapid growth or reparative hyperplasia after trauma, bleeding, etc., even a small polyp may contain some epithelium which by itself histologically resembles that of the more orderly malignant tumors. The morphology of small samples of a large polyp may over- or undervalue quantitatively the histologic features suggesting potential malignancy. The morphology of polyps removed *in toto* is evaluated readily by multiple sampling.

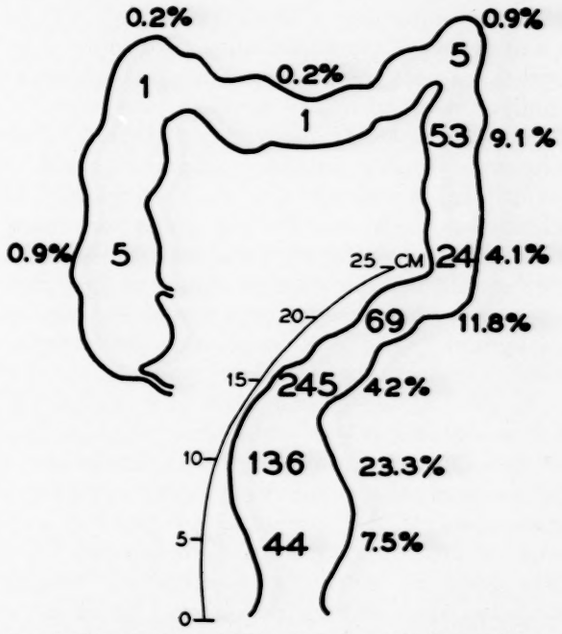


FIG. 1. Distribution of 583 polyps found in 401 patients.

Every polyp or piece of polyp should be made to yield adequate samples in number proportional to size; if the stalk or base is present, this should be sampled also. The final clinical impression of probably malignant behavior is based upon the histology of the lesion *and* on gross findings. Bearing these points in mind, Dr. Eleanor Humphreys devised and adhered to the following working classification for the purposes of this study, not for general diagnostic use:

1. *Polypoid nodule or thickening on fold:* Localized hypertrophy with mild deformities of crypts and surfaces.

2. *Hyperplastic polyp:* Hypertrophy and hyperplasia of the cells, glandular elements and surfaces, constituting a distinct, usually sessile polyp with retention of the crypt patterns and staining of the glandular units in the adjacent mucosa. The number of basally placed nuclei may be increased, but not greatly.

3. *Benign adenomatous polyp or hyperplastic and adenomatous (mixed) type:* A distinct polyp, sessile or pedunculated, manifesting phenomena of active growth. These include basophilic hyperchromatism, crowding of nuclei; loss of

cytoplasmic mucus; distortion of glandular patterns; increased mitotic activity; formation of many small glandular buds from the sides of the crypts and papillary fronds at their mouths.

4. *Benign (?) adenomatous polyp:** This diagnosis implies probable benignancy, with random samples containing a small percentage (10 to 15 per cent) of glandular units with some characteristics of those prevailing in adenoma malignum.

5. *Malignant (?) adenomatous polyp:** This diagnosis implies possible malignancy, with a significant percentage (15 to 30 per cent) of glandular units manifesting some or many characteristics of the adenoma malignum group. On purely cellular characteristics of the most abnormal units, these polyps would be rated as malignant. On total evaluation of samples clinical malignancy seems very unlikely.

6. *Adenoma malignum:* Adenoma malignum, i.e., malignant polyp—equivalent to carcinoma *in situ*, intramucosal carcinoma or grade I adenocarcinoma; manifesting exaggerations and distortions of the adenomatous pattern with marked crowding, upward displacement, pleomorphism of nuclei and enhanced mitotic activity. Areas of such polyps may be identical with those of the less anaplastic colonic adenocarcinomas which have invaded the bowel wall. There is no invasion of the stroma other than by the buds which form new acini, tubules and crypts as the polyp grows. The term adenoma malignum is a useful one for a histologically malignant polyp whose potential invasiveness is unknown.

7. *Papilloma:*† Broad-based polyp with greatly elongated simple or branching crypts separated by delicate stroma and forming villous efflorescences at the surface. Lateral buds are absent or few. Cell types vary as in benign and malignant adenomas. Progressive growth is in area more than in height.

8. *Carcinoma:* A glance at the section establishes this diagnosis. The only exception is an early adenocarcinoma which has not yet invaded the stalk or base of an adenoma malignum. The criteria include a high degree of anaplasia and pleomorphism; complex and often imperfect glandular units; high abnormal nuclei; nucleoli and mitotic figures; and local invasion of stroma by neoplastic cells.

* Intermediate categories: Benign (?) and malignant (?) diagnoses are based on recognition of the fact that errors in interpretation may depend on sampling at proctoscopy or when the specimen is prepared for histologic evaluation. These categories also take into account the fact that cellular features of malignancy may be present during the periods of unusually active normal growth, such as, during reparative hyperplasia.

† "True" papilloma: Adjectives such as papillary, papillomatous and villous are, of course, applicable to the adenomatous tumors whose stalks branch repeatedly to become "mulberry" or "cauliflower" polyps or whose surfaces are papilliferous or villous.

TABLE VII
HISTOLOGIC DIAGNOSES OF ORIGINAL POLYPS IN 352 PATIENTS WITH SINGLE POLYPS ON INITIAL EXAMINATION

	No. of Patients	Incidence (%)
Polypoid nodule	8	2.2
Hyperplastic polyp	48	13.6
Adenomatous polyp	141	40.0
Benign ?	35	9.9
Malignant ?	18	5.2
Adenoma malignum	67	19.0
Carcinoma	10	3.0
Carcinoid	1	0.3
Inflammation	4	1.1
Leiomyoma	2	0.6
Lipoma	3	0.8
No specimen	15	4.3
Total	352	

Histology: Present Study. Single polyps were present in 352 of the 401 patients found to have polyps at the initial examination. The histologic diagnoses are indicated in Table VII. Of the 352 patients 297 returned for follow-up examination (84.4 per cent); 82 new polyps were found in 57 patients (19.2 per cent). The histologic diagnoses are listed on Table VIII.

The forty-nine remaining patients in the original group of 401 had more than one polyp at the initial examination (12.2 per cent); this figure is lower than that of Enquist and State[2] who found multiple polyps in 32.7 per cent on initial proctoscopic examination. The histologic diagnoses of original multiple polyps are listed in Table IX. Thirty-eight of the forty-nine patients (77.6 per cent) returned for follow-up examination; 17 (44.7 per cent) had developed new polyps. The microscopic appearance of the subsequent polyps is indicated in Table X. These findings indicate that a patient who has had a polyp is almost four times as prone to new polyp formation as the individual without polyps; furthermore, the patient with multiple

polyps at the initial examination is more than twice as likely to develop additional lesions on subsequent study as persons with single polyps initially; and he is eight times more prone to develop new polyps than the "average" patient attending a gastrointestinal clinic. (Table XI.)

TABLE VIII
HISTOLOGIC DIAGNOSES OF NEW POLYPS IN FIFTY-SEVEN PATIENTS WHO INITIALLY HAD SINGLE POLYPS BUT WHO DEVELOPED NEW POLYPS

	No. of Polyps	Incidence (%)
Polypoid nodule	3	3.7
Hyperplastic polyp	11	13.4
Adenomatous polyp	51	62.2
Benign ?	2	2.4
Malignant ?	5	6.2
Adenoma malignum	7	8.5
Carcinoma	1	1.2
Inflammation	1	1.2
Lipoma	1	1.2
Total	82	

The distribution of histologic diagnoses in the four groups (Tables VII to X) appears not to indicate a definite trend. The incidence of carcinoma in polyps was highest in the small

TABLE IX
HISTOLOGIC DIAGNOSES OF 102 ORIGINAL POLYPS IN 49 PATIENTS WITH MULTIPLE POLYPS ON ORIGINAL EXAMINATION

	No. of Polyps	Incidence (%)
Polypoid nodule	5	4.9
Hyperplastic polyp	13	12.5
Adenomatous polyp	36	35.0
Benign ?	10	10.0
Malignant ?	11	10.8
Adenoma malignum	15	15.0
Carcinoma	5	4.9
Inflammation	3	2.9
Lymphatic nodule	4	4.0
Total	102	

group of patients who had multiple polyps originally and who subsequently developed new polyps. (Table X.) Since these patients had had a thorough proctoscopic examination at the time the original polyp was discovered, we assume that the subsequent polyps developed during the interval between the first and second observations. Although the new polyps apparently were of recent origin, two were unequivocally carcinomatous, suggesting their origin as carcinoma rather than as transition from a benign polyp.

TABLE X
HISTOLOGIC DIAGNOSES OF THIRTY-TWO POLYPS IN SEVENTEEN PATIENTS WITH MULTIPLE POLYPS ON ORIGINAL EXAMINATION WHO DEVELOPED NEW POLYPS ON SUBSEQUENT EXAMINATION*

	No. of Polyps	Incidence (%)
Polypoid nodule	..	....
Hyperplastic polyp	4	12.5
Adenomatous polyp	14	43.8
Benign ?	2	6.2
Malignant ?		
Adenoma malignum	3	9.3
Carcinoma	2	6.2
Inflammation	1	3.1
No specimen	6	18.7
Total	32	

* These seventeen represent 44.4 per cent of the multiple polyp group followed (thirty-eight patients). Six of the seventeen patients had multiple polyps on re-examination.

For control purposes proctoscopy also was repeated within six months to five years in 316 patients (Table XI) selected at random from those with an initial normal examination; 17 polyps were found; this incidence (5.4 per cent)

TABLE XI
INCIDENCE OF POLYPS AND CARCINOMA OF THE COLON

	Polyps (%)	Carcinoma (%)
Routine Gastrointestinal Clinic patient	5.4	2.1
Control group (initial proctoscopy normal)	5.4	3.1
"Single polyp" patient	19.2	9.4
"Multiple polyp" patient*	44.7	20.4

* Not including multiple polyposis

is identical with that in the original group of 7,487 patients.

RELATIONSHIP OF POLYPS AND CARCINOMA

Many authors have emphasized the close relationship between polyps and carcinoma,

based on the following types of evidence: (1) frequent co-existence of the two lesions, (2) similar pattern of anatomic distribution and (3) apparent transition of a benign polyp to obvious carcinoma.

TABLE XII
BENIGN POLYPS ASSOCIATED WITH CANCER OF THE COLON

Author	No. of Cases of Cancer of the Colon	Material	Per cent with Polyps
Buser (1950)[29]	478	Clinical and surgical	7.9
		No autopsy material	
David (1940)[30]	128	Surgical	13.0
Dukes (1925)[31]	33	Surgical	75.0
Helwig (1947)[22]	25	Autopsy	52.0
Lahey (1952)[32]	3,000	Surgical	25.0
Lawrence (1936)[24]	67	Autopsy	27.1
Mayo (1942)[25]	334	Autopsy	34.1
Mider (1946)[33]	726	Multiple carcinoma	38.0
		Single carcinoma	17.0
Moore (1951)[34]	92	Autopsy	33.0
Stewart (1931)[26]	79	Autopsy	26.6
Susman (1932)[27]	34	Autopsy	44.0
Swinton (1947)[28]	195	Autopsy	25.1

Polyps in Patients with Cancer of the Colon. The frequent co-existence of polyps in patients with cancer of the colon has ranged in various reports from 8 to 75 per cent. (Table XII.)

Carcinoma in Patients with Polyps. DeMuth et al.[35] found carcinoma of the colon in 36 per cent of patients with polyps; Sandusky and Parsons[36] in 13.8 per cent; and Buie et al.[37] in 8 per cent of 1,640 patients. In the present study carcinoma of the colon was found in 43 of the 401 patients with polyps, an incidence of 10.7 per cent.

Anatomic Distribution. Many authors have been impressed with the similar anatomic distribution of polyps and carcinoma.[12,22] On the other hand, Lawrence[24] and Susman[27] found the greatest number of carcinomas in the sigmoid, while the polyps were rather regularly distributed throughout the large bowel. The reason for this difference is not apparent.

Transition of Benign Polyps to Obvious Carcinoma. The direct transition of benign polyps to cancer seems less conclusively established although individual reports have stressed this development. Buie and Brust[38] re-examined 19 of 143 individuals with solitary adenomas of the rectum and lower sigmoid after an interval of two to ten years. In eleven the adenoma had been removed at the original examination; in none was there evidence of recurrence or the development of other polyps. In three instances the untreated adenoma appeared to have increased in size during the interval of three to four years. One other untreated adenoma presented no change in gross appearance after three years. Four untreated persons, however, were found to have carcinoma superimposed upon the site of the previously noted adenoma. Since the histopathology of the original polyp was not known, the possibility that the four polyps were carcinomatous at the time of initial examination cannot be excluded. The histologic demonstration of small focal areas of carcinoma without invasion in an otherwise benign adenomatous polyp may indicate malignant transformation rather than neoplasm from onset, as many investigators have emphasized.[14,22,29] On the other hand, we have been unable to find conclusive direct evidence of the observed transition of a completely benign polyp to carcinoma. This type of evidence would be extremely difficult to obtain since a biopsy from one area of a polyp may be benign and yet the remaining unbiopsied portion could conceivably manifest malignant changes; it is well known that biopsies from different areas of a polyp may reveal varying portions of normal and abnormal cells. Thus separate biopsies of the same lesion at different times may suggest initially a benign process and later a carcinoma; such information would not necessarily prove that the lesion was totally benign originally and later underwent neoplastic transformation. Colvert and Brown[8] have concluded that malignant polyps are either malignant at origin or become malignant early in their course, and that benign polyps do not undergo neoplasia with the passage of time; in their series the incidence of carcinoma after five years was the same among patients in whom polyps were not removed as in a group treated by complete removal of the polyps.

Relationship of Carcinoma to Polyps in the Present Study. There were forty-three carcinomas of the colon among the 401 cases. The sex distribution in this group is approximately similar; the age of the patients with carcinoma was definitely higher than in the polyp group. The locations of the lesions are shown in Table XIII. Seventy-seven per cent of the carcinomas were in the sigmoid or below; 23 per cent were in the proximal colon, a figure greatly exceeding that for the location of the polyps. Thus the location of polyps and carcinoma as determined clinically is similar but by no means identical.

The incidence of carcinoma of the colon in the 7,086 patients without polyps was 2.1 per cent. The incidence of carcinoma in the 401 polyp

patients was 10.7 per cent, five times greater than in the non-polyp patients. This figure includes carcinoma found prior to the discovery of the polyp in nine cases (2.2 per cent); carcinoma (not including adenoma malignum or carcinoma *in situ*) in the polyp itself in fourteen cases (3.5 per cent); carcinoma co-existing with the polyp in thirteen cases (3.4 per cent); and carcinoma of the colon found some time after the discovery of the original polyp in seven cases (1.7 per cent). The total number of patients found to have carcinoma after discovery of the original polyp undoubtedly would be higher if the follow-up studies were entirely compiete. The seven cases of carcinoma found in the follow-up examination of 335 polyp patients represent an incidence of 2.1 per cent. This figure is almost identical with the incidence of carcinoma in the entire series of 7,086 patients seen in the gastrointestinal clinic who did not have polyps, and at first glance might suggest that polyp patients are no more likely to develop carcinoma subsequently than are other gastrointestinal patients. However, since the average age of this group of cancer patients was approximately seven years older than the polyp patients, the further lapse of time may reveal a higher incidence of carcinoma in the polyp group.

TABLE XIII
LOCATION OF CARCINOMA OF THE COLON IN FORTY-THREE CASES ASSOCIATED WITH POLYPS

	No.	Per cent
10 cm. (rectum)	6	14.0
10–15 cm. (rectosigmoid)	11	26.0
Above 15 cm. (sigmoid)	16	37.0
Descending colon	1	2.3
Splenic flexure	1	2.3
Transverse colon	2	4.6
Hepatic flexure	2	4.6
Ascending colon	2	4.6
Cecum	2	4.6
Total	43	....

The relationship of carcinoma to single and multiple polyps also is of interest. There were thirty-three carcinomas in 352 patients with a single polyp originally (9.4 per cent). Carcinoma was found in ten of the forty-nine patients with multiple polyps originally (20.4 per cent), suggesting that patients with multiple polyps are twice as likely to develop carcinoma as individuals with a single polyp.

FATE OF POLYPS WITH EARLY MALIGNANT CHANGES WHEN LOCALLY EXCISED

There is general agreement that the small benign rectal polyp below the peritoneal reflection can be removed safely with either a biopsy forceps, direct fulguration or, if it is pedunculated, by the high frequency electric snare. Benign polyps above the peritoneal reflection are removed locally only when they are small and easily accessible; otherwise these lesions are removed at abdominal operation. The type of therapy is influenced also by the clinical condition and age of the patient. The decision as to the proper treatment of polyps with early histologic evidence of carcinoma (adenoma malignum; adenocarcinoma, grade I; or carcinoma *in situ*) is more difficult because of the natural desire to avoid radical procedures, such as abdominoperineal resection, except when absolutely necessary. The adequacy of local treatment may be questioned when the pathological report of a low-grade malignancy is returned in the absence of fixation, ulceration, induration and firmness as clinical evidence of malignancy. The hazards of local removal are emphasized by Welch, McKittrick and Behringer.[40] In an analysis of 152 cases from the literature and thirty-four personal cases with polyps of the rectum or colon histologically containing cancer, and treated by local excision only, metastases or recurrent carcinoma developed in thirty-one patients or 17 per cent of this group. All these had papillary adenomas or adenomatous polyps of high grade malignancy. There were no recurrences among individuals with adenoma malignum or adenocarcinoma, grade I. Welch et al. further point out that in lesions removed locally with the subsequent pathologic diagnosis revealing high grade malignancy, some degree of assurance can be obtained by frequent proctoscopic examination, since lymph node metastases occur infrequently unless recurrence can be demonstrated locally. They report nine cases with recurrences; only one had a positive lymph node in the absence of local recurrence. McLanahan et al.[41] stress a wider utilization of the principle of local surgical excision in the conservative management of certain adenomas showing malignant change.

In the present group of 401 polyp patients 312 lesions (78 per cent) were removed with biopsy forceps or snare, 73 (18 per cent) surgically and 16 (4 per cent) were not removed initially.

(Table XIV.) Recurrent polyps were noted in eight cases treated by local excision. Seven of the recurrent polyps were discovered and removed within three to six months after the first proctoscopy; one was removed three years

TABLE XIV
METHOD OF TREATMENT AND FOLLOW-UP OF 401 POLYP CASES

	Total	Per cent
Local removal at proctoscopy	312	78.0
Follow-up	262	
No follow-up	50	
Surgical excision	73	18.0
Follow-up	62	
No follow-up	11	
No treatment	16	4.0
Follow-up	11	
No follow-up	5	
Total number of cases	401	100.0
Total number of cases with follow-up	335	83.5
Total number of cases with no follow-up	66	16.5

Subsequent Polyps Found at Follow-up

Patients with subsequent polyps after local removal at proctoscopy	62	23.7
Patients with subsequent polyps after surgical excision	12	19.4
Total number of subsequent polyp cases found at follow-up	74	22.0

after the initial examination. The histologic appearance of the new polyps did not differ significantly from the original lesion nor did any of these develop unequivocal carcinoma with or without metastases at follow-up examination.

The clinical course of untreated polyps would constitute significant information but most of the polyps were removed at the initial examination. The entire series contains only sixteen such patients; eleven returned for study. The polyps originally varied in size from 0.2 to 1.5 cm. and were located from 2 to 20 cm. above the anal ring. In four of the eleven patients there was no evidence of the previously described polyp; in each case the polyp had measured less than 4 mm. in size; one may thus speculate as to the possible disappearance of small polyps or so-called mucosal excrescences.[7] The original polyps were demonstrated in the remaining seven patients after periods of one to five years. Only one polyp had increased in size; six were removed locally at the re-examination; one was not removed because of the advanced age of the patient. A focal area of adenoma malignum was noted in one polyp. The remaining lesions were benign adenomatous polyps.

SUMMARY

In 7,487 patients undergoing proctoscopic and x-ray examination during the period January 1, 1947, to December 31, 1951, the incidence of polyps was 5.4 per cent; 92.8 per cent were diagnosed by proctoscopic examination; x-ray examination was necessary in 7.2 per cent. The average age of the patient was fifty-two years; males predominated in a ratio of 3.5:2. Symptoms and physical findings were of minor diagnostic importance; most of the polyps were demonstrated at "routine" proctoscopy. Approximately 73 per cent of the polyps were located in the distal 15 cm. Approximately 68 per cent of the polyps were less than 1 cm. in size; of these 16.7 per cent were less than 3 mm.

Detailed histologic comparison of the original and new polyps revealed no demonstrable significant trend toward malignancy. The incidence of adenoma malignum was no greater in the group of patients with subsequent polyps than in the original group. However, the incidence of carcinoma was highest in patients with multiple polyps originally who subsequently developed new polyps. Follow-up examination revealed new polyps in 19.2 per cent of the patients with single polyps initially, and in 44.7 per cent of those with multiple polyps originally. Thus the tendency to new polyp formation was fourfold greater among "polyp patients" than in persons without polyps. Patients with multiple polyps on initial examination appeared eight times more likely to develop new polyps than normal individuals. The incidence of carcinoma of the colon in the 7,086 patients without polyps was 2.1 per cent; in the 401 polyp patients it was 10.7 per cent. There were 33 carcinomas in 352 patients with a single polyp originally (9.4 per cent). Carcinoma was found in 10 of the 49 patients with multiple polyps originally (20.4 per cent). There were 13 instances of carcinoma coexisting with polyps (3.4 per cent); in 7 patients (1.7 per cent) a carcinoma of the colon was found some time after the discovery of the original polyp.

The polyps were removed at proctoscopy in 312 patients (78 per cent); surgical excision was

required in 73 (18 per cent); in 16 patients (4 per cent) the polyps were not removed initially. Follow-up examination was obtained in 262 of the 312 patients treated by local removal (83.9 per cent); recurrent polyps were discovered and removed in from three to six months in 8 patients (3 per cent). The histologic appearance of the original and recurrent lesion was similar, suggesting that local excision did not increase the likelihood of malignant transformation. Sixty-two of the seventy-three patients (85 per cent) treated by surgical excision returned for re-examination; none had demonstrable recurrence of the lesion. Eleven of the sixteen patients untreated originally returned for re-examination; in four there was no evidence of the previously described polyp; in each instance the polyp had been estimated as less than 4 mm. in size. The original polyps were again demonstrated after a period of one to five years in the remaining seven patients. Six of these polyps were removed locally at the time of re-examination; one was not removed because of the advanced age of the patient. One polyp contained a focal area of adenoma malignum; the remaining lesions were benign, adenomatous polyps.

CONCLUSIONS

1. Polyps of the rectum and sigmoid are found in approximately 5 per cent of adult patients undergoing "routine" proctoscopic examination.

2. New polyps develop in approximately 20 per cent of patients with one polyp originally and in 40 per cent of those with multiple polyps. The histologic appearance of the new polyps does not differ significantly from that of the original lesion.

3. Carcinoma of the colon and rectum occurs with five times greater frequency in "polyp patients" than in normal individuals. Patients with multiple polyps are twice as likely to develop carcinoma as individuals with a single polyp.

4. The incidence of recurrence of polyps after local removal appears to be low.

5. No conclusive direct evidence was obtained in this study to prove that benign adenomatous polyps undergo transition to carcinoma.

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Seminars on Liver Disease

The Meaning of Liver Function Tests*

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DURING the past ten years few significant additions have been made to the array of tests in general use to assess the functional status of the liver. Indeed, the experience of the last decade has led to the obsolescence of many of the more cumbersome procedures, and has given increasing prominence to those that can be performed rapidly, inexpensively and accurately with minimal hardship to the patient and with economy of time and effort to the investigator. Each clinic continues to employ a preferred battery of tests but there is increasing unanimity as to which are to be included in routine investigations. Standardization of methodology, however, has not kept pace, and case reports continue to be in part valueless unless the technics employed and the normal range for each determination are specifically stated.

It is not intended in a sketchy discussion such as this to mention or explain all liver function tests, or to state their relative merits or indicate a preferred directive for their determination. Countless references are available that cover this aspect of the subject.[1] Instead, a few familiar tests will be selected to exemplify the complexity of hepatic physiology and to point out the fragmentary speculative knowledge on which many of them are based.

All hepatic function tests depend upon activities of the liver which can be expressed quantitatively. Any attempt to compare the value of one procedure with that of another, or to correlate the extent of a functional derangement with the histologic alterations must necessarily fail. Each hepatic function represents the over-all summation of integrated enzyme systems which are not as yet subject to quantitative study, and which are known to be modified not only by the vigor and mass of hepatic parenchyma, but also by (1) the availability of specific metabolites, (2) the supply of oxygen to the cells, (3) the presence or absence of factors that enhance or depress specific enzymes in the system and (4) the activity of other organs within the body. An example of some of these complexities may be found in the conjugation of benzoic acid with glycine to form hippuric acid, an activity which was, and still is, widely employed as a liver function test. The recent work of Schachter and Taggart[2,3] indicates that this seemingly simple conjugation can be carried out *in vitro* in the following two steps:

$$\text{(1)}\quad \text{Benzoic acid} + \text{coenzyme A} + \text{ATP} \xrightleftharpoons[\text{activating enzyme}]{} \text{benzoyl-coenzyme A} + \text{AMP} + \text{inorganic pyrophosphate}$$

This reaction, therefore, is dependent on the activity of coenzyme A, energy-rich phosphate bonds generated by aerobic metabolism, and a specific activating enzyme.

$$\text{(2)}\quad \text{Benzoyl-coenzyme A} + \text{glycine} \xrightarrow[\text{glycine N-acylase}]{} \text{hippuric acid} + \text{coenzyme A}$$

The second reaction exhibits the unusual phenomenon of product inhibition, that is, the velocity of the reaction is strikingly decreased by low concentrations of either of the products, hippuric acid or coenzyme A, despite the fact that thermodynamic considerations would indicate that the reaction should proceed eventually to completion. These workers have also pointed out that the reaction depends upon the presence of a specific enzyme "glycine N-acylase" which they have purified from liver tissue and have shown to transfer acyl groups from coenzyme A to glycine, but to no other amino acid. It is suggested by these observations that, *in vivo*, the hippuric acid test depends on proper availability in the liver of benzoate, specific enzymes, high energy phosphate bonds, adequate supply of oxygen and glycine, and the removal of inhibiting substances from the reacting system. Each of these requisites involves the orderly participation of other

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separate and distinct metabolic activities. Superimposed is the excretion of hippuric acid by the renal tubules which, in turn, depends upon specific enzymatic coordination in an organ other than the liver.

Disease processes, such as neoplastic infiltration, that cause focal depletion of functioning tissue, may be quite extensive before decrease of hepatic activity is detectable, since reserve capacity is so great that 80 per cent of the liver can be removed without serious consequences. On the other hand, disorders with diffuse derangement of the blood supply to the liver, or with impediment of the outflow of bile or lymph, or with impairment of metabolic functions affecting the viability or physiologic activity of hepatic cells, commonly invoke symptoms and give rise to patterns of disturbances which are characteristic and of diagnostic aid. In all cases, however, the laboratory findings should be correlated with the general features and progressive course of the disease, for diverse pathologic processes often give rise to similar types of derangements, and function tests are but indices to be incorporated in the general clinical appraisal.

DYNAMICS OF THE HEPATIC PARENCHYMAL BARRIER

The liver should be regarded as an organ complex with metabolic and excretory activities depending upon the anatomic and functional integration of (1) parenchyma, (2) biliary tree and (3) mesenchymal elements, composed chiefly of sinusoidal endothelium and supporting structural framework. Each of these systems may be selectively deranged by disease but more frequently a disturbance in one is reflected by dysfunction in the others. Many examples of these chains of deleterious events may be cited; perhaps the most important from the point of view of clinical consequences is the irritating effect of necrotizing lesions of the parenchyma upon the mesenchymal tissues. Recent studies on the structure of the human liver re-emphasize the well ordered anatomic relationship of parenchymal, biliary and mesenchymal elements. Elias[4] and his co-workers have pointed out that the hepatic parenchyma is arranged in a three-dimensional labyrinthine system of sheets or "plates" of unicellular thickness. The polygonal cells in this arrangement vary in size and configuration like mortised stones with five, eight, ten or twelve facets to conform to the complex undulations and intertwinings of the hepatic plates. Each cell is so shaped as to have maximal surface exposure to the vascular channels (sinusoids) which pervade all portions of the parenchymal complex. The bile capillaries, or spaces into which the various constituents of bile are excreted, lie as intercommunicating networks between the surfaces of contiguous polygonal cells. It is obvious that any necrosis of parenchyma, or any factor that disturbs either excretion or absorption at this interface, may affect the volume and composition of bile. Structural studies such as these indicate that the liver parenchyma, in essence, represents a barrier of cells[5] separating the vascular bed from the biliary system, with a functioning surface in direct contact with each. All measurable activities of the liver depend upon the capacities of this barrier of cells to maintain interchange of metabolites with both compartments. The coordination of these activities in health is remarkable, and such substances as bile pigments, bile salts, colloidal dyes and water are excreted by the parenchymal cells into the bile spaces, while a regulated exchange of metabolites such as sugars, fats, proteins and their derivatives is maintained at the other interface between cell and portal blood.

Indeed, one important aspect of normal liver function might be defined as the orderly "discrimination" by the hepatic parenchyma of those substances to be excreted in the bile from those maintained in dynamic equilibrium with the rest of the body through the circulation.

HYPERBILIRUBINEMIA

The term, bilirubin, is generally employed by clinicians to designate the several forms of iron-free pigment present in the blood which are ultimately derived from the breakdown of hemoglobin constantly taking place in the reticulo-endothelial system of the body. This pigment occurs normally in the blood in amounts that rarely exceed 1 mg. per 100 ml. because of the regulating excretory activity of the liver. An occasional person with physiologic hyperbilirubinemia has a higher excretory threshold without any evidence of hepatic disease or of excessive red cell breakdown. Studies on the excretion of fluorescein by the liver indicate that substances analogous to bilirubin are removed from the blood by the parenchymal cells as a specific activity and are transported across the barrier and excreted in aqueous solution into the

bile capillary spaces.[6] Little is known of the factors involved in the transport and excretion of bilirubin but it can be assumed to represent cellular energy involving enzyme activities. The excretion of bilirubin by the parenchyma can be inhibited by causing death to the cells or by depressing cellular metabolic activities by a variety of injurious processes such as anoxia, poisoning, viral infections, chronic malnutrition, and perhaps specifically by non-toxic agents, such as methyl testosterone.[7] Elevation of pressure in the biliary system also inhibits the excretion of bilirubin, possibly by preventing the passage of water into the biliary spaces.

The numerous dysfunctions leading to the development of jaundice continue to provoke controversy, especially the mechanistic concepts indicating that obstructive jaundice is caused by hydrostatic dilatation and rupture of the bile capillaries with the leakage of bilirubin back from the biliary system into the lymphatics of the liver and thence to the blood stream. Direct observations have shown the prompt appearance of bilirubin in thoracic duct lymph after ligature of the common duct in dogs,[8] and lend support for the possible back-flow of the bile from the biliary to the lymphatic system in obstructive jaundice, but alternate mechanisms must also be considered. Grafflin and Chaney[9] have recently studied obstructive jaundice in mice by direct visualization of the liver during the excretion of fluorescent substances after ligature of the common duct and have noted no dilatation of the bile capillaries and no evidence of leakage into the lymphatics. It was also noted that soon after obstruction was produced the hepatic cells failed to take up the dye, and little could be found excreted in the biliary system.

Much emphasis has been placed upon the fact that with obstructive jaundice the van den Bergh reaction becomes positive, and it has been generally stated that the direct-reacting form represents bilirubin that has been excreted by the liver and has regained access to the circulation. A number of recent workers[11] have challenged this assumption and, furthermore, have questioned the validity of the van den Bergh reaction as an indication that two distinct forms of bilirubin, the "direct" and "indirect" reacting fractions, actually exist. On the other hand, the recent work of Najjar and Childs,[12] who have succeeded in crystallizing an indirect-reacting bilirubin, supports the original assumption of two forms. Furthermore, Cole and Lathe[13] have separated two fractions by chromatography and have noted that the direct-reacting component, in addition to being excretable by the kidney, is more soluble in aqueous solution, migrates more rapidly on the chromatographic column, and has distinctive light absorption properties. Both pigments form complexes with the proteins of the serum but these workers have suggested that it is the insolubility of the indirect-reacting form, and not the nature of the protein binding, which determines its failure to react in the diazo reaction without the addition of alcohol.

The mechanisms by which indirect-reacting bilirubin is converted to the direct form in both obstructive and hepatocellular jaundice continue to be a baffling theoretical problem, although it is generally accepted that the finding of more than a trace of prompt direct-reacting form of the pigment in the blood is never normal and always indicates an hepatic or biliary derangement. Some workers assume that when the transport of bilirubin from the sinusoids to the bile capillaries is impaired bilirubin may enter and leave the hepatic cells at the vascular interface or that transformation may take place at the cell surface. Others have indicated that activating substances such as bile salts, organic alcohols and enzymes may enter the blood stream in various forms of hepatic disease and bring about extracellularly the transformation of naturally occurring indirect-reacting bilirubin to the water soluble, metal-pigment complex giving a direct reaction. Attempts to establish these various hypotheses by mixing sera giving direct and indirect reactions or adding purified bilirubin to serum have only added emphasis to the artifacts inherent in the diazo reaction when used to quantitate the two forms of bilirubin. The results depend upon the concentration of the two pigments, the pH of the medium, the colorimeter used, the protein complexes formed, and upon the concentration of accessory substances in the blood. From the practical standpoint, however, the quantitation of the prompt direct-reacting fraction, the one-minute bilirubin of Ducci and Watson,[14b] and the estimation of the total serum bilirubin is of usefulness in the detection of certain types of hepatic disturbances, and in following the clinical course of a jaundiced patient.

Many other problems related to jaundice remain unsolved. The question is often asked why, with complete obstructive jaundice, the serum bilirubin does not continue to rise. Elim-

ination by the kidneys of the prompt direct-reacting fraction does not of itself furnish an adequate explanation. The possibility must be raised that there are mechanisms within the body for the degradation of the four-pyrrole pigments which play a role in the regulation of the serum bilirubin level when normal excretion is blocked. Quantitative investigations to test the fate of bilirubin and its derivatives with methods now available are beset with great technical difficulties, for many members of the group are relatively unstable and slight changes taking place within the body or as a result of manipulations of the investigator lead to an array of transformations affecting color, solubility, and physical and chemical properties. Despite intensive studies, the significance of many of the pyrrole compounds described in health and disease is still open to question.

Another more practical aspect of the jaundice problem is the failure of icterus to develop in partial biliary obstruction or when extensive loss of hepatic tissue is present, and also the lack of parallelism between the serum bilirubin level and the serum alkaline phosphatase in hepatic disease. It is important to bear in mind that the bilirubin level in the blood and that of the alkaline phosphatase are probably maintained at normal levels by different excretory mechanisms. The blood is cleared of bilirubin, both direct and indirect-reacting fractions, so long as sufficient normal functioning hepatic tissue remains. The same is true for alkaline phosphatase but from a mechanistic standpoint more hepatic units seem to be required to maintain normal alkaline phosphatase clearance than bilirubin clearance. Hence, as an obstructive process develops a rise of serum alkaline phosphatase usually appears before hyperbilirubinemia. This discrepancy is of clinical usefulness, and the finding of hyperphosphatasemia in a non-jaundiced patient is often the first indication of intrahepatic tumor, abscess or extrahepatic lesions causing sustained partial occlusion of the common duct.[14a]

DERANGEMENTS OF PROTEIN METABOLISM

The synthesis of serum albumin, prothrombin and fibrinogen has been shown to take place exclusively in the hepatic parenchyma. Many other constituents of the serum protein complex no doubt are derived from the same source. The site of origin of the serum globulins, especially those in the gamma fraction, is more obscure but is probably in the reticulo-endothelial system as a whole, of which in man, next to the bone marrow the liver is the largest member.

As would be expected, many diseases of the liver give rise to alterations of the protein complex, some of which are so characteristic that they are of considerable diagnostic value. Decrease of functioning hepatic parenchymal mass, as seen in neoplastic replacement, chronic biliary obstruction, chronic passive congestion, etc., is often manifested by a decreased serum albumin level. When inflammatory changes are not part of the liver disorder, few notable quantitative or qualitative changes are found in the gamma globulin fraction. The low albumin levels characteristic of hepatic insufficiency represent, in part, a shift in balance between the anabolic and catabolic activities of the liver, for the parenteral administration of supplementary serum albumin gives only a temporary rise, and the loss of serum albumin by hemorrhage or paracentesis is promptly replaced to the original level. But sustained return to normal figures is seen only when restoration of hepatic function is attained.

Many disorders of the liver are inflammatory in nature. Acute and chronic necrotizing lesions of parenchymal cells due to many causes incite secondary reactions in the mesenchymal tissues. Likewise, primary infections of the liver, (viral, bacterial or protozal) cause inflammatory and proliferative reactions in these structures. Furthermore, many idiopathic systemic diseases of the reticulo-endothelial system, such as Boeck's sarcoid, infectious mononucleosis and splenic anemia cause reactions in the intra- and perilobular connective and endothelial tissues. The histologic evidence of mesenchymal involvement may vary from slight swelling or increase in numbers of histiocytes to marked cellular infiltrations, granuloma formation or deforming proliferations of reticulum cells and fibroblasts throughout the liver. Inflammatory reactions in the hepatic stroma usually cause a rise in the gamma globulins of the blood, some of which are abnormal in that they are notably precipitable by solutions of various heavy metals, thymol, distilled water, etc., and are detected clinically by standard tests using substances such as Hayem's solution, zinc sulfate and buffered thymol as precipitating agents. Other abnormal globulins are detectable by their excessive attachment to specific surfaces such as red cells, colloidal gold or cephalin-cholesterol emulsion particles. Special claims have been made for the

clinical usefulness of the various flocculation and turbidity tests. For example, in cirrhosis the zinc sulfate turbidity[15] is said to be markedly elevated despite only a moderate rise of the thymol turbidity. In toxic and infectious hepatitis, however, the sensitivity of the two tests is often reversed.

The zinc sulfate test is perhaps the most accurate in determining total serum gamma globulin irrespective of special properties or of its source in the body. The test is not specific for hepatic derangements but Harris[16] and her associates have pointed out its special value in differentiating, in the newborn, jaundice due to parenchymal dysfunction from icterus caused by congenital malformation of the bile ducts. Elevated zinc turbidity, when present, is indication of hepatocellular jaundice and warrants months of watchful medical management rather than surgical exploration, which is always a hazardous procedure in the jaundiced infant.

The cephalin flocculation reaction differs in mechanism from the globulin precipitation tests in that the stabilizing factors in the serum are of prime importance.[17] The reaction is a fortuitous one in that human serum diluted 1:20 contains sufficient gamma globulin potentially to cause flocculation of a cephalin-cholesterol emulsion, but normally there are sufficient amounts of stabilizing components in the serum complex to prevent the flocculation from taking place. Hence, a negative reaction indicates dominance of stabilizing components. If normal serum is made progressively more dilute, i.e. 1:80, the stabilizing activity is depressed more rapidly than the flocculating effect, and a negative reaction can be converted to a positive reaction in any normal serum by sufficient dilution. The stabilizing components of the serum have not been identified with certainty but consist of labile, lipid-rich constituents of the electrophoretically derived albumin—alpha-1-globulin fraction. Its activity deteriorates rapidly after partial purification and more slowly in whole serum even at icebox temperatures. Because of the instability of the stabilizing factors and the stability of the gamma globulins, normal serum preserved for several weeks in the unfrozen state gradually undergoes changes to give a positive reaction. The stabilizing factors disappear from the serum within forty-eight hours after acute parenchymal injury and remain absent until hepatic healing is well established. Following brief episodes of injury due to acute anoxia or mild viral hepatitis or sublethal poisoning, a positive cephalin flocculation test may be present for a few days only and promptly return to normal. Rapid transitions in the test suggest that the stabilizing factors, like alpha globulins, have a short half-life. The failure of the liver with necrotizing lesions or acute parenchymal damage to synthesize these substances would lead to prompt depletion in the blood and gives rise to a positive cephalin flocculation reaction.[18] The same effect would be produced by elaboration by the injured liver of an inhibitor of the stabilizing factors or to drastic reorientation of constituents of the serum complex, but no factual data are available to establish or exclude any of these possible mechanisms.

The cephalin flocculation reaction is not a true liver function test. Correlations with the histologic changes in hepatitis and cirrhosis indicate that, in most instances, it reflects acute necrotizing lesions of hepatic parenchyma, especially those that incite mesenchymal irritation; but not necessarily, for a similar derangement is found in acute malaria[19] when the parenchymal cells and the connective tissues appear essentially normal. The test does not indicate the extent of hepatic damage nor does it become positive in all forms of cellular injury. For example, the test is usually negative in obstructive jaundice unless secondary infection is superimposed, neoplastic replacement, fatty metamorphosis, chronic passive congestion except in acute exacerbations, solitary abscesses and hyaline degeneration. Positive reactions are observed in about 90 per cent of cases of viral hepatitis and in about 80 per cent of cases of toxic hepatitis. Unless there is concurrent involvement of parenchyma, the cephalin flocculation test is negative in cholangitic hepatitis, biliary cirrhosis or cholangitis. The test is of value in distinguishing active cirrhosis in which parenchymal breakdown is taking place from inactive forms with healed fibrotic lesions.[21] The test may be negative, and thereby misleading as to the extent of hepatic damage, in cases of fatty liver undergoing degenerative or even cirrhotic changes. To elicit a positive test hepatic cells usually must be undergoing autolysis. When destruction is complete, as in the centers of the lobules in chronic passive congestion, the reaction becomes negative.

In hepatic derangements the cephalin flocculation reaction does not seem to depend primarily upon hyperglobulinemia or upon the

presence of abnormal globulins. Instances occur, however, in other conditions in which a positive reaction is due to peculiar reactivity of the gamma globulin fraction with the cephalin cholesterol emulsion particles. For example, the sera of all normal laboratory animals except the monkey give a positive reaction and it has been found that in these instances no amount of stabilizing fraction abolishes flocculation. A similar change in gamma globulin has been found in certain human sera with positive flocculation reactions, especially in patients with infectious mononucleosis, hemolytic jaundice, disseminated lupus erythematosus, pernicious anemia, acute leukemia, chronic malaria, bacterial endocarditis and diffuse diseases of the reticulo-endothelial system. On the other hand, not all diseases of the reticulo-endothelial system give rise to this type of globulin change, since multiple myeloma, Hodgkin's disease and chronic leukemia seldom give a positive cephalin flocculation reaction.

The cephalin flocculation test is not specific for any clinical condition. A positive reaction indicates the possibility of at least two types of abnormality in the serum protein complex, and liver disease or reticulo-endothelial disturbances can be distinguished only by correlation with other tests and by a survey of the over-all clinical picture. Routine employment of both the cephalin flocculation reaction and the thymol turbidity or the zinc turbidity test has been recommended since possible disturbances in the serum protein complex can be missed by using but one test. The cephalin flocculation reaction is of especial value in recognizing acute parenchymal derangements of hepatitis or cases of acute poisoning before globulin changes have developed. On the other hand, late hepatitis and other chronic irritative lesions may be associated with positive thymol turbidity or zinc turbidity tests which indicate increases or alterations of the gamma globulin fraction after the cephalin flocculation test has returned to normal.

Paper electrophoresis has recently been applied clinically to the quantitative study of the altered serum protein patterns in disease and gives promise of being a convenient and useful tool for the study of the liver. By this method the chief disturbances in the albumin and globulin fractions can be readily recognized. However, special tests will probably continue to be needed to detect all the subtle distortions in the serum protein complex, such as redistribution of lipoproteins, or changes in iron-combining proteins, or the absence of copper-protein complexes known to take place during hepatitis or to be associated with special types of liver derangements.

SERUM ALKALINE PHOSPHATASE

Less is known about the mechanisms underlying the regulation of the serum alkaline phosphatase level in the blood than perhaps any other of the important liver function tests. The origin of the enzyme is still controversial. Its identity as a single substance has not been established and the mode of excretion by the liver is not known. Nevertheless its value as an index of biliary obstruction is generally recognized despite the fact that, for causes yet not clear, the test, like all the others, is not entirely trustworthy. Serum alkaline phosphatase is generally recognized as a product of osteoblastic activity. Histologic staining for enzymatic activity in the liver reveals practically none in the normal parenchymal cells. However, the Kupffer cells and those of the bile canaliculi contain demonstrable evidence of alkaline phosphatase action.[20] It can be inferred that if the hepatic cells elaborate the enzyme or transport it from blood to the bile spaces it is in an inactive form or in too low concentration for histologic detection. As has already been stated, alkaline phosphatase is probably excreted by a different mechanism than bilirubin, for marked accumulation does not occur in the blood in acute yellow atrophy when the patient is deeply jaundiced and few viable parenchymal cells remain in the liver. On the other hand, obstruction of the biliary tree, with the exception of terminal bile capillaries, leads to a gradual retention of alkaline phosphatase in the blood. The test is notably misleading in brief episodes of obstructive jaundice such as with acute cholangitis or cholecystitis. In rare instances it fails to rise proportional to the degree of jaundice in chronic extrahepatic obstruction. Nonetheless, the combination of a negative cephalin flocculation test with rising serum alkaline phosphatase and deepening jaundice is the most accurate indication of obstructive jaundice that has yet been devised. The test is also useful in the investigation of enlargement of the liver, for expanding intrahepatic lesions of all kinds may cause moderate elevation of serum alkaline phosphatase without other demonstrable changes. Hepar lobatum also may often be distinguished from Lannec's cirrhosis by a notable elevation of the

serum alkaline phosphatase in the presence of a hard irregular liver, as syphilitic scarring tends to cause more narrowing and obliteration of the biliary tree than a diffuse process. The serum alkaline phosphatase is also not infrequently elevated in the early stages of hepatitis when the liver is enlarged and tender and the increased internal pressure causes compression of the smaller bile ducts. In contrast to obstructive jaundice, however, it is characteristic for the serum alkaline phosphatase to decrease during the course of hepatitis, even as the serum bilirubin levels continue to rise. In the cholangitic forms of hepatitis and in diffuse cholangeolitis a more persistent elevation is noted. All forms of cirrhosis may lead to constriction of the biliary radicals and thereby cause elevation of serum alkaline phosphatase; Laennec's cirrhosis rarely, coarse nodular cirrhosis not infrequently, and biliary cirrhosis practically always.

In the presence of osseous lesions such as Paget's disease and hyperparathyroidism the serum alkaline phosphatase values are useless in hepatic studies. Children also may have unpredictably high levels in the blood. It is regrettable that several systems of unitage for serum alkaline phosphatase are in use at the present time: Bodansky, King-Armstrong and others. It is therefore essential that the method employed be mentioned in all reports.

BROMSULFALEIN

This dye is probably excreted by the parenchymal cells in a manner similar to bilirubin. Except for serial comparisons, the test is therefore useless in most cases of non-hemolytic jaundice since dye retention can be anticipated. Bromsulfalein excretion is perhaps the most reliable of tests to assess the total functioning hepatic mass in the non-jaundiced subject. The test is not a specific measure of either metabolic or excretory activity of the liver, for loss of tissue and depression of parenchymal vigor, venous shunts that by-pass the liver and obstructive processes in the biliary tree may all lead to abnormal retention of the dye. Caroli has demonstrated by duodenal aspiration that dye retention due to obstructive factors is manifested by a slower appearance of bromsulfalein in the biliary secretion than when retention is due to deficiency or functional impairment of hepatic tissue.

The bromsulfalein test is usually carried out by giving 5 mg. per kg. body weight and noting the retention of dye after forty-five minutes. One of the obvious disadvantages of this method which affects the accuracy of the procedure is the relatively excessive amounts given to obese or edematous patients.

The dye may also be administered at a measured rate to maintain blood levels at an arbitrary constant. Such a procedure is laborious and is not recommended for routine clinical use but by employing it, combined with catheterization of the hepatic vein, Bradley[23] and his collaborators have been able to measure the hepatic blood flow in human subjects under various conditions of health and disease, and have succeeded in estimating the splanchnic blood volume by indirect calculations. Theoretical loss of bromsulfalein in the reticulo-endothelial tissue and seepage into extravascular spaces, and loss in the urine, has not been found significant by direct measurement.

BLOOD CHOLESTEROL AND CHOLESTEROL-ESTER RATIO

Cholesterol is probably synthesized in many tissues, especially the liver and intestinal wall. Much has been learned by isotopic technics of the processes by which this relatively complex steroid structure may be synthesized from acetate by liver tissue and then further converted to bile acids and other derivatives. The blood cholesterol level depends in part upon thyroid activity, intercurrent infections, hereditary factors, etc. Nevertheless, the total serum cholesterol and the percentage of esterified cholesterol may be used as hepatic function tests since the liver is the chief regulating organ by which the synthesis, esterification, degradation and excretion of cholesterol takes place in the body. Depression of parenchymal activity usually causes lowering of serum cholesterol, particularly of the esterified fraction in the blood. Obstructive jaundice, on the other hand, usually gives rise at first to increase of free cholesterol with some elevation of cholesterol esters. In long-standing cases of biliary obstruction, as hepatic damage develops and the synthesis and esterification of cholesterol becomes depressed, total cholesterol falls, due especially to the drop in cholesterol ester. Cholangeolitic involvement as seen in toxic cholangitis and biliary obstruction causes striking elevations of serum cholesterol. The same may also be seen in acute viral cholangitic hepatitis; however, inflammation of the portal triads does not affect in all

cases the functioning of the cholangioles contained in the diseased surrounding structures.

The cause of the rise in blood cholesterol in biliary obstruction is not understood, for the small amount excreted normally in the bile does not represent the chief regulatory process by which cholesterol levels are maintained in health and disease. The rate of synthesis of cholesterol in liver slices has been shown to be modified by increase or decreases of various ingredients of the metabolic pool. The feeding of cholesterol, for example, depresses the conversion by the liver tissue of acetate to cholesterol. It is therefore a strong possibility that the specific metabolic readjustments brought about by biliary obstruction lead to the accumulation of substances which affect both the rate of synthesis and the metabolic fate of cholesterol and related steroids in the body.

Closely related to the problems of cholesterol synthesis and degradation by the liver are those involving the regulation of biologically active steroids derived from the adrenal cortex and reproductive systems. Evidence has been advanced from many sources that common features of hepatic disease, such as the retention of salt and water, changes in sex characteristics, the development of spider angiomas, etc., indicate disturbances in the orderly conjugation, degradation and excretion of the hormones maintained by the normal liver. The methods available for the precise study of these complex activities are so limited that only vague generalizations are justifiable at the present time. Indeed, if deranged metabolism of steroids is the cause of certain clinical features of liver disease, it has been most difficult to correlate the extent of the disturbance with any other liver function test or with any type of structural alteration.

SERUM ENZYMES AS AN INDEX OF HEPATIC FUNCTION

Another notable feature of cholesterol metabolism is the observation by Sperry[25] that esterification with fatty acids continues in incubated fresh serum for a number of hours, due to the presence in the blood of a specific esterifying enzyme. This phenomenon has been confirmed and amplified by Turner[26] who has pointed out that the cholesterol-esterifying activity of serum is diminished in hepatitis and other types of parenchymal derangement; and the decrease parallels so closely the severity of the process that it may be employed clinically as an index of functional impairment. Choline esterase activity of serum is also depressed proportionately to the severity of parenchymal dysfunction[27] and has been recommended as a method to distinguish obstructive from hepatogenous jaundice Further search will no doubt reveal other enzymatic activities in the blood that reflect the status of the liver.

Decreases of serum choline esterase or of cholesterol esterase give rise to no clinical symptoms but it has been suggested that the liver may maintain the orderly functioning of other organs by enzymatic control. Hepatic coma, for example, has been attributed to failure of the conjugation of ammonia and glutamic acid to form glutamine within the nervous tissue when hepatic failure develops. There is no evidence at the present time that the normal process of detoxification of ammonia by the nerve cells is maintained by hepatic enzymes, despite the fact that no toxic agent in the blood during hepatic coma has been isolated which would explain a breakdown in the metabolism of ammonia.

SUMMARY

A few illustrations have been cited to indicate the complexities involved in the simplest conventional liver function tests. It is indeed surprising that in view of the multiple derangements found in most diseases of the liver these tests can be reliable or of any clinical value. Decrease of functioning hepatic mass can be assessed, however, the presence of destructive and inflammatory processes in the liver can usually be recognized, and the factor of biliary obstruction evaluated. Important clues as to the nature and severity of the disease process can thus be derived. Furthermore, by repetition of pertinent tests from time to time the course of the derangement can be followed and the value of therapy can be checked. Tests only become meaningful when the concept of the liver as a dynamic regulator of specific excretory and of integrated metabolic activities is kept in mind.

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Conference on Therapy

Drugs in the Diagnosis of One of the Curable Forms of Hypertension

THESE are stenographic reports slightly edited of conferences by the members of the Department of Pharmacology and of Medicine of Cornell University Medical College and New York Hospital, with collaboration of other departments and institutions. The questions and discussions involve participation by members of the staff of the college and hospital, students and visitors. A selected group of these conferences is published in an annual volume, Cornell Conferences on Therapy, by the Macmillan Company.

DR. HARRY GOLD: A point that has emerged from the experience of recent years with patients in whom the blood pressure is elevated is that hypertension does not label a disease but a number of diseases with different life histories and differing courses. Technics of one kind or another have been developed in the endeavor to separate the various groups of cases which belong together. One device which has proved particularly useful is the reaction to certain chemical agents as a means of differential diagnosis among the hypertensive diseases. How these matters stand has been made the subject of this conference. Dr. Richard E. Lee will open the discussion.

DR. RICHARD E. LEE: I think it is well to limit my remarks to an aspect of the subject which has received particular attention in the past few years, that which has to do with the use of drugs in hypertensive patients for the purpose of ruling out a pheochromocytoma. These agents belong to the group of substances known as adrenergic blocking agents. There is one, histamine, which is not a member of this group but which is of diagnostic value in some cases.

How common is the pheochromocytoma? Our own experience is quite limited but there are data from groups of workers with extensive experience in this field which might be mentioned. One figure often quoted is that of Smithwick's group in Boston. At operation in 1,200 cases of sympathectomy he discovered six cases of pheochromocytoma, an incidence of 5 per 1,000. There is a report from the Mayo Clinic that among 32,500 persons with high blood pressure there were clinical features suggesting pheochromocytoma in 585. Among this group of suspects twenty-seven were found to have the tumor, an incidence of approximately 1 per 1,000 among hypertensive individuals. On the basis of these values and the incidence of hypertension, one can suspect that in the population of the New York Metropolitan area there are to be found somewhere between 300 and 800 cases of pheochromocytoma.

What are the signs which bring the patient under suspicion of having this type of tumor? The first case which came to our attention about five years ago had a normal blood pressure under ordinary conditions. The possibility of tumor came up as a diagnostic problem only while she was under anesthesia for cholecystectomy and her blood pressure suddenly rose so high that it pushed the mercury in the manometer beyond the limits for recording. Clearly then, a normal blood pressure reading does not necessarily exclude pheochromocytoma, although all six cases that we have seen here had either episodic or sustained hypertension. All had tachycardia. Four patients in whom the blood sugar level happened to be determined showed hyperglycemia. This is understandable since one of the functions of epinephrine is to mobilize the blood sugar. At least two of these latter patients had been treated with insulin as diabetics for a period of several years because of their glycosuria and diabetic type of glucose tolerance test. All the patients complained of headaches. In the two cases with episodic hypertensive crises, the headache was of a violent pounding type associated with nausea, vomiting and pallor of the skin. An abdominal tumor was palpable in five of the six patients. These, then, are the symptoms or findings which direct one's attention to the possibility of pheochromocytoma: episodic or sustained hypertension, tachycardia, headaches, glycosuria, hyperglycemia, attacks of nausea and vomiting, pallor of the skin and abdominal tumor.

Of the pharmacologic agents used in differentiating cases of pheochromocytoma from other illnesses, the benzodioxanes are the most popular. They are referred to as the Fourneau compounds, of which there are two general types, one represented by 883F which blocks both circulating epinephrine and the effects of sympathetic nerve stimulation; the other represented by 933F which predominantly blocks the effect of circulating epinephrine. Compound 933F is the one that has been most widely employed to aid in the diagnosis of pheochromocytoma. Its use is based on the observation that after injection of this material administration of epinephrine leads to an abrupt fall rather than to a rise of the blood pressure. Benzodioxane® therefore appears selectively to block the vasopressor action of epinephrine, leaving the vasodepressor action intact. Since pheochromocytoma is a tumor presumably releasing epinephrine into the bloodstream, injection of benzodioxane is followed by a significant fall of the blood pressure in patients with pheochromocytoma. Only a positive response is to be taken as of value. Failure to obtain the depressor reaction is less reliable as a diagnostic index since there are cases of pheochromocytoma in which the typical response fails to occur. Some of the reports show more optimistic results than others, but, however that may be, the fact remains that there are cases of pheochromocytoma which are not detected by the benzodioxane test as carried out in the conventional manner; and when the patient presents features suspicious of pheochromocytoma and the benzodioxane test fails to confirm it, we are in the habit of repeating the test with another of the diagnostic agents. Benzodioxane is not free of disagreeable side effects. It stimulates the central nervous system. The patient sometimes becomes disoriented. It often produces a very marked tachycardia, and an increase in the blood pressure in hypertensive subjects without the tumor, of a degree that is sometimes threatening. These effects are so disturbing that we have discontinued the routine use of this test in the Out-Patient Department.

There have been trials of other adrenergic blocking agents to aid in the diagnosis of pheochromocytoma but they seem on the whole to be less satisfactory. Dibenamine,® a compound related to the nitrogen mustards, also produces adrenergic blocking, both to injected epinephrine and to sympathetic nerve stimulation. It may cause a fall of blood pressure in pheochromocytoma but the effect is much too prolonged and the compound gives rise to local irritation at the site of injection. Priscoline,® chemically related to some of the antihistaminic agents, exerts a similar dual pharmacologic action; and while it sometimes produces a satisfactory fall of the blood pressure in pheochromocytoma, its effects have not been constant and its use has not become popular. The same applies to tetraethyl ammonium chloride.

Histamine has been advocated for the detection of pheochromocytoma, especially in patients who usually have a normal blood pressure but who may be subject to episodic rises as the result of the secretion of epinephrine by the tumor. The intravenous injection of histamine causes a fall of blood pressure in normal persons, but in those with the epinephrine-secreting tumor the drop in blood pressure calls forth compensatory vasoconstrictor responses of such magnitude as to produce a very marked secondary increase in blood pressure. The intravenous administration of histamine, however, is not an altogether safe procedure and epinephrine should be at hand during the test.

Finally, I should like to say a word about regitine,® one of the most recent additions to the list of drugs useful for the diagnosis of pheochromocytoma. This material is effective as an adrenergic blocking agent not only by intravenous and intramuscular injection but also by oral administration. It possesses the dual action of blocking sympathetic constrictors as well as the constrictor effects of epinephrine and nor-epinephrine. It has a somewhat longer duration of action than benzodioxane, several minutes to several hours, and this point is advantageous since the effect of benzodioxane is so transient that the observer may miss it. Another advantage of regitine over benzodioxane is the fact that its use is not accompanied by a rise in blood pressure in those patients with hypertension who do not have pheochromocytoma. However, it causes tachycardia, probably primarily the result of a moderate fall of the blood pressure which may obtain in essential hypertension. Experience to date has been fairly satisfactory with this compound. Grimson reported observations in four cases of pheochromocytoma in which he found that intravenous administration of this drug causes a fall of the diastolic pressure of more than 25 mm.

Hg. This is regarded as a positive response to regitine. The group at the Mayo Clinic reported on five cases of pheochromocytoma tested with this agent. In two of these, in whom the blood pressure was labile, the intramuscular dose was without effect at a time when the blood pressure was normal but caused a satisfactory fall of the blood pressure during a period when the control blood pressure was elevated. In the other three cases of proven pheochromocytomas with sustained hypertension the results with intramuscular injection were not as satisfactory as those after intravenous trials. Two of these cases yielded "false negative" results after the intramuscular dose but all three showed positive responses with sharp and sustained fall of the blood pressure when the drug was given intravenously. Two conditions have been observed to alter the response to regitine in such a way as to suggest pheochromocytoma in patients with hypertension who do not have the tumor (the "false positive"), namely, severe uremia and prior administration of barbiturates. Barbiturates should be withheld for at least twenty-four hours before the test is made.

I am inclined to the view that histamine is the best test drug at the present time to rule out pheochromocytoma in a suspect who has a normal blood pressure or labile blood pressure. and that regitine is the most satisfactory one for pheochromocytoma suspects with sustained hypertension.

DR. GOLD: Before we proceed with questions from the audience, would you be willing to take up step-by-step precisely what you do when you are confronted with a patient with hypertensive disease in whom, for one reason or another, the possibility of pheochromocytoma comes up?

DR. LEE: The first thing we do is to sit down with the patient and talk things over. The patient may not show hypertension at the time. The first case of pheochromocytoma that we saw had a normal blood pressure. We discovered a large abdominal tumor which turned out to be a pheochromocytoma. She was previously treated for two years in the outpatient department of a large hospital as a case of neurosis with anxiety because of such symptoms as pallor of the skin and lips, nausea, vomiting and violent bursting headaches. After we learn of such symptoms we ask whether the patient has ever been told of having sugar in the urine. We then, of course, proceed with a full physical examination and determination of the blood sugar. An account of such factors as I have just mentioned, with or without elevated blood pressure, is sufficient reason for a provocative test with one or another of the drugs. We do not test every patient with elevated blood pressure but only those who, because of these particular features, become a tumor suspect.

DR. GOLD: Now for the details of the test.

DR. LEE: Because of the possibility of severe side reactions, we reserve benzodioxane for use only when the patient is in the hospital, but we have no hesitation in using regitine in the outpatient department. The patient is placed flat in bed. An intravenous infusion of 5 per cent dextrose is started, and the blood pressure is taken at intervals until it becomes stabilized for a period of at least fifteen minutes. We then inject 2.5 mg. of regitine into the lumen of the rubber tubing close to the needle over a period of ten seconds. Immediately after the injection the blood pressure is taken at intervals of thirty seconds for about five minutes, the readings being made as quickly as possible. In the absence of pheochromocytoma the diastolic pressure falls somewhat, occasionally as much as 20 mm. It returns to the previous level in two or three minutes, sometimes going 10 or 15 mm. above the previous level. This drug does not produce such very marked increases in the diastolic pressure, 30 to 50 mm. Hg, as occasionally follow the intravenous injection of benzodioxane. The systolic pressure may or may not fall. If there is no response after the first dose of regitine, we repeat the injection with 5 mg. ten minutes after the pressure is again stabilized. If the fall is less than 25 mm., you are relatively safe in saying that there is little evidence for suspecting the tumor. I am not aware of any "false negative" responses to intravenous regitine at the present time, although it is likely that such cases will be encountered.

DR. WALTER MODELL: What is the use of the dextrose solution?

DR. LEE: Its purpose is really to provide a means for injecting the drug after the blood pressure has stabilized without having to give the patient a venipuncture. The stick of the needle sometimes greatly disturbs the level of the pressure.

DR. GOLD: Dr. Lee, you have said what constitutes a negative response indicating that the patient does not have pheochromocytoma. What is the unequivocal positive response?

DR. LEE: A positive response is a fall in the diastolic pressure of more than 25 mm. of Hg

lasting for a period of from five minutes to two or three hours, usually with a fall in systolic pressure of comparable degree. It is a type of response which is not easy to miss.

DR. GOLD: Are there any questions?

DR. SEYMOUR H. RINZLER: I note that Dr. Lee advocates doing the test for pheochromocytoma only in patients in whom such symptoms as pallor, sweating, nausea and vomiting arouse suspicion. There are those who believe that the test should be done as a routine in all cases of hypertension, even those with a fixed elevation of the blood pressure and without these episodes of special symptoms. I wonder if there is not something to be said for such a practise in view of the fact that the patient stands a chance of complete cure by operation should the hypertension prove to be due to pheochromocytoma.

DR. LEE: I believe this recommendation is based on Smithwick's report in which he seems to have stumbled on six cases of pheochromocytoma during operations in 1,200 cases. It is assumed that these patients did not have a suspicious history, although I do not believe that Dr. Smithwick ever actually stated that these six patients might not have been suspected from an appropriate history. I think that pheochromocytoma is too infrequent a condition and the drugs at present available have not been proven to be of sufficient specificity and reliability to justify routine testing with one of these agents in every patient with hypertension. The group at the Mayo Clinic, who have had the most extensive experience in this matter, applies the test only in about one of every sixty cases of hypertension, those with a suspicious history and findings. I am inclined to agree with this view for the present.

DR. MCKEEN CATTELL: In connection with the action of the sympathetic blocking agents that come under consideration in the tests for pheochromocytoma, I think it is well to call attention to the fact that the receptor cell is the site of action and that this results in a block not only to circulating epinephrine but also to the material liberated by stimulation of sympathetic nerves. I doubt that there is any fundamental distinction between the mode of action of the different members of this group, although it is a fact that it requires higher concentrations of the particular blocking agent to produce its effect in relation to epinephrine liberated at the endings than in relation to injected epinephrine.

DR. MODELL: Is there any explanation for the "false positive" results?

DR. LEE: I don't know of a satisfactory explanation. Perhaps in some cases the agent produces relatively marked blockade of adrenergic nerve impulses and a resultant hypotension via this mechanism.

DR. GOLD: I suppose what you mean is that the dividing line between a positive and negative response which you have placed at a blood pressure drop of 25 mm. is not as sharp as it seems, and that there is some overlapping of cases with and without pheochromocytoma. Occasional cases without pheochromocytoma may show a drop greater than 25 mm. and occasional cases with pheochromocytoma will show a drop smaller than 25 mm.

DR. MODELL: How do you explain the "false negative" responses to regitine to which you referred in connection with intramuscular injections?

DR. LEE: On the probable basis of insufficiently rapid absorption from intramuscular injection, making that route of administration less reliable in these particular cases.

DR. GOLD: Dr. Lee, do you happen to know of any cases in which the result of the test with a drug like benodaine® or regitine was used to decide the question of pheochromocytoma, in which the patient was operated upon, and in which it was found at the operation that he did not have a pheochromocytoma?

DR. LEE: Yes, I have seen one such case. There are several others in the literature.

DR. GOLD: Do you know whether it is a frequent occurrence?

DR. LEE: No, I do not.

VISITOR: I wonder whether the "false negative" and "false positive" responses to these drugs are not really due to the simple fact that all that one is measuring is a fall of the blood pressure and that a fall may be produced in those without as well as in those with pheochromocytoma. Such factors as individual differences in susceptibility to the drugs, dosage and the amount of epinephrine the tumor may be delivering then easily explains why some people without the tumor respond as if they had one and others with the tumor respond as if they did not have one.

DR. LEE: I think you are right. The differentiation which the drug makes between the two kinds of cases by the difference in degree and duration of blood pressure fall is not qualitative but quantitative in nature. One can see these factors at work among hypertensive patients who do not have a pheochromocytoma; some are very reactive to these agents and others are

relatively insensitive. Such variability is inherent in any biological reaction.

DR. GOLD: We have invited Dr. Goldenberg of the College of Physicians and Surgeons of Columbia University to participate in this discussion and we are privileged to have him here. He has developed an important aspect of the differential diagnosis of pheochromocytoma.

DR. MARCEL GOLDENBERG: I might start at the point at which the discussion has been left, namely, the problem of "false negative" and "false positive" responses to the drugs. It is interesting to note that thus far there have been no "false negative" responses to regitine reported, although I personally believe that such responses are not decided by the kind of drug used but by the stage of the disease in which the test is made.

When we began to look into the nature of the problem of pheochromocytoma with persistent hypertension, we had the notion that hypertension under these circumstances might be comparable to the effects of a prolonged infusion of epinephrine. We were quite surprised when we learned of such a case from Smithwick's department showing a "false negative" response to the drug. We analyzed the tumor of this patient and found in it a considerable amount of epinephrine. This patient at one time presented the classical symptoms of pheochromocytoma—hypertension, tachycardia, sweating and high basal metabolic rate, about +64. By the time she was readmitted the whole picture had changed. She still had severe hypertension with eyeground changes but the basal metabolic rate was now normal and there was no tachycardia. The thought came to us at this time that the patient with pheochromocytoma might enter a stage where the elevated blood pressure is no longer humoral. We then followed the course of a group of patients with pheochromocytoma and persistent hypertension after removal of the tumor and found that in seven of twelve cases the hypertension persisted for varying lengths of time, days to years, after the tumor had been taken out. One may safely assume that in such cases the mechanism responsible for hypertension after the tumor was removed was similar to the mechanism operating while the tumor was still in the patient's body. This means that the hypertension of patients with pheochromocytoma is not always directly caused by the secreted epinephrine or nor-epinephrine. It seems that in some way the exposure of the human body to excessive amounts of epinephrine and/or nor-epinephrine for long periods of time gives rise to a lasting hypertensive reaction which persists after the source is removed. There is perhaps an analogy in experimental unilateral renal hypertension in which the blood pressure is elevated as the result of constriction of one renal artery and may remain elevated after the kidney is removed.

Cases of pheochromocytoma fall into several clinical groups. There are those with the classical signs of paroxysmal hypertension, the so-called adrenal sympathetic syndrome; those with persistent hypermetabolism or hyperglycemia and intermittent hypertension; and those with marked persistent hypertension, elevated basal metabolic rate and glycosuria. This last symptom complex occurs when large amounts of epinephrine or nor-epinephrine are continuously being secreted. The real problem relates to the intermediary group, those cases in which there are few or no symptoms other than persistent hypertension, for they closely resemble the conventional case of essential or malignant hypertension. It may be assumed that in these instances the tumors are small and secrete norepinephrine, or that the patient is in the nonhumoral stage of the disease in which the benzodioxane or the regitine test is negative. I have a mental reservation about the explanation which is offered by the group at the Mayo Clinic for the "false negative" response to intramuscular regitine. It may not be poor absorption but a case of testing the patient in the nonhumoral phase of the disease. While it is true that the results are more uniformly positive with intravenous regitine, there is also the danger that the intravenous route might give rise to "false positive" responses. I believe the danger of this is reduced by Dr. Lee's inclusion of the duration of the response in his definition of the "positive response." A very fleeting fall of the diastolic pressure, even as much as 50 mm. Hg., would indicate essential hypertension rather than pheochromocytoma.

We have been following patients with pheochromocytoma by studies of urinary excretion of epinephrine and nor-epinephrine. I believe that this is the best method available at the present time for establishing the diagnosis. The patient with pheochromocytoma excretes more catecholamine than the normal, and the difference is quite marked. The method is applicable to cases of both persistent and paroxysmal hypertension. In this connection I should mention the fact that in one group of eleven cases of pheochromocytoma the results of urinary excretion tests matched

those of pharmacologic tests; whenever the excretion tests were positive, the benzodioxane and regitine tests were also positive, and in those in which the histamine test was made it also was positive. It is well known, however, that the histamine test quite frequently yields "false positive" responses and some of the other pharmacologic tests have yielded both "false positive" and "false negative" responses. The urinary excretion test is especially valuable as a means of establishing that a positive response is not a "false positive." We found that in pheochromocytoma with persistent hypertension the urinary excretion of epinephrine or nor-epinephrine is persistently high, about 2,000 μg. in twenty-four hours, while in cases with paroxysmal hypertension the urinary excretion may be only slightly elevated between paroxysms, these showing increased excretion during the paroxysm. The normal excretion of catecholamines is about 40 μg. of nor-epinephrine equivalent in twenty-four hours. Some cases of essential hypertension excrete up to 100 μg. in twenty-four hours. We have eliminated the bio-assay and replaced it by fluorometric determination of catecholamines.

In a suspect in whom the pharmacologic test may represent a "false negative" response the presence or absence of pheochromocytoma can be established by provoking secretion of epinephrine or nor-epinephrine through the injection of histamine. I agree with Dr. Lee that a single pharmacologic test often is not conclusive.

DR. GOLD: It seems from this that the use of benzodaine or regitine alone for the diagnosis of pheochromocytoma may lead us into error and that the results of the pharmacologic tests may have to be checked by urinary excretion values for epinephrine and nor-epinephrine.

DR. FRANK C. FERGUSON: I should like to question whether the proof is sufficient that regitine is more specific or really better than other compounds that have been tried for the diagnosis of pheochromocytoma. It seems to have been tried more in humans than in animals. It belongs to the same chemical class as priscoline and has several actions besides that of adrenergic blocking. May not the enthusiasm for it be due to the fact that it is simply one of the newer compounds and so new that we do not yet know enough about what is wrong with it?

DR. LEE: Regitine is, to be sure, relatively new but as far as we have gone it appears to be quite satisfactory and for the most part free of those disagreeable effects which we have been in the habit of seeing with such compounds as the benzodioxanes. It is far from perfect and I would agree that in the course of time it is likely to be supplanted by better agents.

I should like to add that we have been very much interested in Dr. Goldenberg's technic for the bio-assay of the urine for catechols. This represents the most physiologic approach to the diagnosis of pheochromocytoma. We had one suspect in which the regitine test was positive and when the urine was tested for catechols by Dr. Goldenberg it proved to be negative.

DR. GOLD: May we assume from all that has been said that the urinary excretion of catechol is a more satisfactory test than the pharmacologic one for the diagnosis of pheochromocytoma?

DR. GOLDENBERG: It certainly has advantages. I have already referred to its utility in connection with problems of "false positive" and "false negative" responses to the drugs. About a month ago I saw an example of the problem in Pickering's department. This was a case of pheochromocytoma with a negative benzodioxane test. The urinary excretion of catecholamines was lower than in cases of pheochromocytoma with persistent hypertension but the presence of the tumor was suggested by the fact that it was still distinctly above normal. In this patient hypertension persisted after the tumor was removed and subsequent examination of the urinary excretion showed that the hypertension was not due to circulating epinephrine or nor-epinephrine but to some secondary mechanism.

DR. LEE: I would agree with that. I think it is the best single test for pheochromocytoma.

VISITOR: What is the situation in the non-humoral stage of pheochromocytoma to which Dr. Goldenberg referred? Is the tumor not secreting epinephrine or nor-epinephrine at that time, or does it mean that the body no longer reacts to the secretion?

DR. GOLDENBERG: It seems that the tumor is not secreting because in that situation the hypertension present before operation persists after the tumor is removed, which means that the elevated blood pressure was due to some secondary mechanism.

DR. GOLD: What are the concentrations of epinephrine or nor-epinephrine that you found in these tumors? We tested two or three of them in the Department of Pharmacology and found vasoconstrictor material in them by the USP method of assay for epinephrine in amounts that were frightening were it all to be liberated into the circulation.

DR. GOLDENBERG: The smallest amounts that we found were about 80 mg., chiefly in the form of nor-epinephrine, and this in two patients who showed a clinical picture like that of essential hypertension.

DR. GOLD: This was 80 mg. in how much weight of tumor?

DR. GOLDENBERG: The concentration was slightly more than 1 mg. per gm. of tumor. There are some which have up to 16 mg. per gm.

DR. GOLD: The upper figure makes a tumor equivalent to a 1.6 per cent solution of epinephrine. One tumor which we analyzed weighed 30 gm. and contained approximately 30 mg. of epinephrine, equivalent to a 1 per cent solution.

DR. GOLDENBERG: I think in your Department of Surgery you had one case of pheochromocytoma in which the tumor contained about 4,000 mg.

DR. GOLD: Yes, I recall that one, we made the analysis. I should like to ask Dr. Goldenberg whether in the cases of pheochromocytoma, which clinically mimic essential hypertension, there is apt to be a greater proportion of nor-epinephrine as against epinephrine in the material secreted by the tumor?

DR. GOLDENBERG: This thought came to us when we first encountered two cases mimicking essential hypertension with small tumors in which the material was almost entirely nor-epinephrine. However, 1 μg. of epinephrine has the metabolic effect of approximately 8 μg. of nor-epinephrine; and if the tumor secretes large amounts of nor-epinephrine, the clinical picture is apt to be one that is quite characteristic of pheochromocytoma, i.e., hypertension with hypermetabolism and hyperglycemia. I believe, however, that most of the cases mimicking essential hypertension represent pheochromocytoma in the non-humoral phase. These are cases that are apt to be negative by pharmacologic tests and are apt to retain the hypertension after the tumor is removed.

SUMMARY

DR. GOLD: In some patients with hypertension the disease is caused by a tumor of the adrenal containing and secreting excessive amounts of epinephrine or nor-epinephrine, the pheochromocytoma. Experience shows this to be the case in about one of sixty patients who present themselves for the problem of an elevated blood pressure. It is possible to cure this form of hypertension in a great many instances by surgical removal of the tumor. The recognition of this special group is therefore a matter of considerable importance. In this conference there were elaborated some of the details of the method by which the diagnosis is made. Much dependence is placed in recent years on a test with drugs which have a characteristic effect in patients with pheochromocytoma. Various so-called adrenergic blocking agents have been used, materials which on injection block the constrictor action of epinephrine or nor-epinephrine circulating in the blood; in consequence of this a fall of the blood pressure occurs rather than the rise seen in patients with hypertension due to causes other than the pheochromocytoma. Most of the discussion revolved around benzodioxane and regitine as the test agents, the conditions under which the test should be made, the details for carrying it out, and the sources of error which might lead one to miss a pheochromocytoma when it is present or assume that it is present when it is not, the so-called "false negative" and "false positive" reactions. There was also some discussion of the intravenous use of histamine in patients suspected of pheochromocytoma by reason of the history of episodes of symptoms but in whom the blood pressure at the time of examination is normal. This drug generally causes a fall of blood pressure but in patients with pheochromocytoma the reaction to this initial effect is a marked secondary rise in blood pressure. One of the interesting features which emerged from the discussion was the view that exposure of the body to excessive concentrations of epinephrine in the form of these secreting tumors may give rise to a permanent form of hypertension. Another development which came in for considerable attention was the use of the urinary excretion of epinephrine and nor-epinephrine as a supplementary test to establish the diagnosis. Patients with this tumor tend to excrete much higher amounts of these catechols and this fact helps to decide the issue in cases in which the results of the drug test are equivocal. It appears to be the practice among some groups to apply these tests in a routine manner in all patients with hypertension, but it was the consensus here that this type of hypertension, while of considerable importance, is not sufficiently frequent to justify that practice. The details of the clinical history by which one comes to suspect the need for carrying out these special tests were brought out.

Clinico-pathologic Conference

Fever of Unknown Origin

STENOGRAPHIC reports, edited by Robert J. Glasser, M.D. and David E. Smith, M.D., of weekly clinico-pathologic conferences held in the Barnes Hospital, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient, W. M. (No. 229168), was a retired white carpenter, sixty-nine years of age, who entered the Barnes Hospital for the first time on November 13, 1953, complaining of weakness, anorexia and fever of six weeks' duration. The family history was non-contributory. The patient's general health had been good for most of his life. Four years prior to admission he had an episode described by his physician as a coronary occlusion. He had been advised to remain in bed for five days and then to resume activity at a decreased level. On occasion he had had dyspnea on exertion but denied orthopnea, ankle edema or paroxysmal nocturnal dyspnea. He had worked as a carpenter for most of his adult life. His diet was adequate; he had smoked one pack of cigarettes daily for many years.

About eleven months before entry the patient had a "flu-like" illness characterized by fever, cough and malaise. He received no specific therapy and recovered uneventfully, but during the illness he noted diminution in size and force of his urinary stream. Because of these symptoms he was referred to a urologist and eight months prior to entry into the Barnes Hospital he underwent suprapubic prostatectomy elsewhere. The excised tissue was examined pathologically and reported as "adenomatous hyperplasia, benign." Following the operation the patient never completely recovered his strength and three months before admission he returned to the urologist complaining of weakness. He was found to have a temperature of 101°F. and was told that he had "pyelitis," but he did not know what drug he had been given. Approximately one and one-half months prior to entry right lower chest pain and a cough productive of small amounts of mucopurulent sputum developed. He consulted an osteopath who prescribed penicillin and chloramphenicol. During this period the patient stated that on occasion his temperature had risen to 102°F. On October 31, 1953, thirteen days before his entry into the Barnes Hospital, he was admitted to another hospital because of fatigue. Apparently the general physical examination was not remarkable. The white blood cell count during the period he remained in the hospital ranged between 7,000 and 9,000 and the patient was told that he was anemic. His sedimentation rate was 32 mm. per hour. Agglutination tests for typhoid, brucella and tularemia were negative. The patient's temperature ranged between 101 and 102.5°F. and was unaffected by therapy consisting of 600,000 units of penicillin and 1 gm. of streptomycin daily over a four-day period. These agents were then discontinued and the patient was given 2 gm. of chlortetracycline for the next four days. Again there was no response. While in the hospital he received one transfusion. Because of failure to improve, he was advised to enter the Barnes Hospital. Additional history obtained indicated that the patient had experienced a 60 pound weight loss during the present illness and had had occasional episodes of vomiting. His cough had increased in severity and had become productive of larger quantities of thick mucoid sputum, but at no time had he had hemoptyses. One week prior to admission urinary incontinence developed and the patient's family stated that at intervals he seemed confused.

Physical examination at the time of admission revealed the patient's temperature to be 39.5°C., pulse 60, respirations 16 and blood pressure 160/60. He was markedly emaciated and dehydrated and appeared chronically ill. He lay flat in bed without dyspnea. A small ulcer was noted under the right eyelid, and several small healed scars on the face marked the site of excision of small skin "tumors." The bones and joints appeared normal. The pupils were small but reacted to light and accommodation and extra-ocular movements were normal. There was no nystagmus. The fundi could not be visualized. A small amount of mucoid discharge

was noted in the left nostril and tenderness was elicited over both antrums. There was no lymph node enlargement nor was the thyroid gland palpable. The chest was symmetrical; on percussion, dullness was present at both bases posteriorly. Rales were heard in the right axilla and at the right base posteriorly. The heart was not enlarged to percussion. The sounds were distant but no murmurs were heard. The abdomen was soft. The liver edge was percussed 6 cm. below the costal margin. One observer stated that the splenic tip was palpable. The genitalia were normal. The anal sphincter was lax. The prostate gland was not enlarged but a firm mass was described on the right anterior wall of the rectum. Neither clubbing nor edema was present. Palmar erythema was noted. Neurologic examination was within normal limits except for diminished knee jerks.

The laboratory data were as follows: red blood cells, 3,580,000; hemoglobin, 10.8 gm. per cent; white blood cells, 5,500; differential: segmented neutrophils, 63 per cent; lymphocytes, 29 per cent; monocytes, 8 per cent. Platelets appeared to be present in normal numbers on the smear. Urinalysis: specific gravity, 1.013; albumin, trace; sugar, negative; porphobilinogen, negative; centrifuged sediment: occasional granular casts per high-power field; culture: negative. Stool: guaiac negative; benzidine positive (2+); cultures (3): no pathogens. Blood chemistry: non-protein nitrogen, 16 mg. per cent; sugar, 59 mg. per cent; potassium, 4.5 mEq./L.; sodium, 133.9 mEq./L.; chloride, 99 mEq./L.; carbon dioxide combining power, 27.5 mEq./L.; total protein, 5.7 gm. per cent; albumin, 2.9 gm. per cent; globulin, 2.8 gm. per cent; acid phosphatase, 1.8 King-Armstrong units; cephalin-cholesterol flocculation test, 3+; thymol turbidity, 2.6 units; sodium bilirubinate, 0.62 mg. per cent; bilirubinglobin, 0.90 mg. per cent; bromsulfalein retention, 18 per cent after forty-five minutes; alkaline phosphatase, 14.6 Bodansky units. Blood cultures (3); negative. Sputum culture: coagulase negative hemolytic staphylococcus albus and neisseria. Sputum examinations (2); negative for acid-fast bacilli. First strength PPD test: negative. Roentgenogram of the chest: left ventricular enlargement and tortuosity of the aorta; pleural thickening along the right lateral chest wall obliterating the right costophrenic angle in the lateral view, with a rounded area of increased radiolucency in the area of the pleural thickening; anteromedial bulge of the diaphragm. Skull films: indeterminate. Electrocardiogram: normal except for prolongation of the Q-T interval. Proctoscopy: negative.

The patient's hospital course was febrile; his temperature was hectic in character and ranged between 38° and 40°c., except when salicylates were given. Despite high fever the pulse rate remained between 70 and 90 per minute and at times was described as dicrotic. Because the patient was unable to eat, on the third hospital day a gastric tube was passed and subsequently alimentation was maintained by this route. Intravenous pyelograms on the fourth hospital day were interpreted as normal. On the same day a lumbar puncture was performed. The initial pressure was 120 mm. of water and the final pressure 100 mm. of water. The fluid was clear and contained only one cell. The protein was 48 mg. per cent, sugar 44 mg. per cent, and chloride 123 mEq./L. Both the colloidal gold curve and Wassermann test were negative as were cultures. An electroencephalogram showed a marked slow dysrhythmia with a left posterior focal trend. It was interpreted as "consistent with an organic basis for the patient's complaints."

On the fifth hospital day the patient was noted to have a hyperactive knee and ankle jerks and a positive Babinski sign on the right, but there was no other change in the physical or neurologic findings. Subsequently he became progressively disoriented and his temperature spiked to 40°c. nightly. On the ninth hospital day, because of the fever and leukocytosis, tetracycline was begun in a dose of 1.5 gm. daily. No significant response occurred. The patient vomited occasionally and at times had diarrhea. Because several observers described the liver as enlarged and tender, on the eleventh hospital day chloroquine was begun in a dose of 0.25 gm. every six hours, and on the thirteenth hospital emetine was added to this regimen. That day there was an increase in the number of rales audible at the right base and a leathery friction rub was heard. Because of tenting of the diaphragm on the right side a diagnostic pneumoperitoneum was performed; no evidence of abnormality within the liver could be demonstrated on the x-ray films taken after introduction of air.

On the fourteenth hospital day the non-protein nitrogen was 80 mg. per cent, sugar 150 mg. per cent, chloride 114 mEq./L., sodium 140.7 mEq./L., potassium 4.7 mEq./L. and the carbon dioxide combining power 21.3

mEq./L. A second stool specimen was again benzidine positive, and a third was both benzidine and guaiac positive. Blood studies revealed a marked left shift without significant leukocytosis.

The patient's obtundity increased, and on the sixteenth hospital day exploratory laparotomy was performed. At operation no abnormalities were noted other than a small amount of whitish, almost clear peritoneal fluid, culture of which showed no growth, and there were a few enlarged nodes in the region of the pancreas. The liver appeared normal but a biopsy of the right lobe was obtained.

Immediately after operation the patient became cyanotic but his color improved after intratracheal aspiration and oxygen therapy. Four hours later his respiratory rate rose to 50 per minute, and he responded only to extremely painful stimuli. Digitalization was begun slowly but because of the development of marked pulmonary congestion he was given lanatoside C and aminophylline intravenously. Despite supportive measures the patient died on November 30, 1953.

CLINICAL DISCUSSION

DR. VIRGIL SCOTT: The problem presented by this case is one of the most interesting and challenging which physicians encounter, namely, the differential diagnosis of fever of unknown origin. The patient, an elderly man sixty-nine years of age, had been ill for some time. Before coming to the Barnes Hospital he had been seen by an osteopath and by several physicians in group practice in a city outside of St. Louis. No satisfactory diagnosis was reached before he was admitted here; and although he remained in this hospital seventeen days and was seen by a number of physicians, a satisfactory diagnosis was never established prior to death. The patient was under the care of Dr. Bruce Kenamore but was also seen in consultation by Drs. Irwin Levy, W. B. Wood and Carl Lischer. The latter performed the exploratory laparotomy which was done just before the patient died. Unfortunately, Dr. Wood and Dr. Lischer are away and we will not have the benefit of their comments but there is a certain amount of information which became available only terminally or after the patient died. Perhaps this additional information will be of assistance in helping us to reach some conclusion. Of importance in the history are the following facts: The patient had had what appeared to be a respiratory infection eleven months before entry and recovered from that illness without specific therapy. Eight months ago prostatectomy was performed, presumably for benign prostatic hypertrophy. It is of interest that the patient never recovered completely his former state of health following that operation. Subsequently, weakness and weight loss were prominent symptoms and fever developed about three months before his admission here. During his illness he received a number of antibiotics, none of which affected his symptoms or course. After he came to the Barnes Hospital one of the most striking features was the hectic fever; his temperature rarely fell below 38°C. and often rose to 40°C., except when the patient was given antipyretics. Associated with the marked fever was bradycardia. In the protocol it was stated that the optic fundi could not be visualized. It is important to add that shortly after the patient was admitted the fundi were well visualized by two different observers and were reported as being entirely normal. There was dullness at the lung bases which persisted and it was thought that the liver was enlarged. One observer believed that he could feel the splenic tip. Although rectal examination at the time of entry suggested the presence of a mass, proctoscopy was entirely negative. Because of the development of certain neurologic changes the patient had at least seven complete neurologic examinations. On six of these it was reported that the Babinski sign was positive on the right. Except for delerium no other neurologic abnormalities were present consistently. Dr. Elliott, would you comment on the x-ray findings?

DR. GLADDEN V. ELLIOTT: The day after the patient entered the hospital a chest film was obtained and a significant amount of pulmonary infiltration was noted in the right lower lobe. The heart and mediastinal structures were shifted toward the side of the infiltrate. In several views fibrotic curvilinear strands, directed toward the right lateral thoracic wall, were present and in one view a calcified pleural plaque was seen. There was irregularity and suggestive narrowing of the right lower lobe bronchus and a curvilinear soft tissue density projecting through the cardiac shadow was thought possibly to represent an inferior mediastinal mass. Considerable attention was given to the bulge in the right diaphragm. It is my opinion that this bulge really was a normal anatomic variant and of no clinical significance. The only other find-

ings in the chest film were calcification of the hilar nodes and tortuosity of the aorta.

Thirteen days after the first radiologic examination diagnostic pneumoperitoneum was performed, in order to delineate further the nature of the anteromedial bulge of the diaphragm. It was demonstrated that the right diaphragm separated cleanly and evenly from the superior surface of the liver which appeared to be smooth. No evidence of a subdiaphragmatic abscess was present. The pneumonitis in the right lower lobe had progressed, however, and a rounded soft tissue mass in the midmediastinum, below the carina but in the immediate vicinity of the right lower lobe, was again noted.

Intravenous pyelograms were also obtained and were negative. Finally, I would like to comment on the skull films. They showed that the pineal gland lay 2 cm. to the right of the midline which deviation is at the upper limit of normal. It was for this reason that the films were reported as indeterminate. Nonetheless, this position of the pineal gland could indicate a space occupying lesion in the left hemisphere. In summary, then, the radiologic findings included chronic progressive pneumonitis in the right lower lobe, a lower mediastinal mass and suggestive narrowing and irregularity of the right lower lobe bronchus. Taking these findings *in toto* they are consistent with the diagnosis of bronchogenic carcinoma and secondary pneumonitis. A metastatic lesion in the left cerebrum cannot be excluded.

DR. SCOTT: Many laboratory tests were performed during the course of the patient's hospitalization. He exhibited a normal white blood cell count and a normochromic anemia throughout the period of observation. The differential was normal until the terminal phase of the illness when a marked left shift developed, the differential showing 17 per cent myelocytes, 3 per cent metamyelocytes, 70 per cent segmented neutrophils amd 10 per cent lymphocytes. Benzidine tests on the stool were reported as positive on three occasions; simultaneous guaiac tests were negative twice and positive once. The patient had hypoalbuminemia without hyperglobulinemia. Liver function tests were of interest in that there was distinct elevation of the alkaline phosphatase, retention of bromsulphalein and a 3+ cephalin-cholesterol flocculation test. Certain negative studies were also of importance—three blood cultures and a urine culture remained sterile, and three stool cultures and a sputum culture revealed no significant pathogens. Agglutinations against the antigens of brucella, typhoid and parathyroid organisms were negative. Smears of two sputa and of gastric washings were negative for acid-fast bacilli. Three stool specimens were carefully examined for E. histolytica by Dr. Tsuchiya and no trophozoites or cysts were found. Because of the patient's obtundity and the positive Babinski sign the spinal fluid was examined and found to be normal in all respects.

The exploratory laparotomy was performed by Dr. Lischer as a last resort. Since he is not here I would like to read his operative note. "Exploration revealed the liver to be slightly enlarged. It was aspirated repeatedly with a large needle and no evidence of liver abscess was obtained. There was no sub-phrenic abscess. No other gross abnormalities were noted within the abdominal cavity except for a few enlarged lymph nodes in the region of the pancreas. The liver was biopsied and the abdomen was closed." Dr. David Smith has given me permission to read the biopsy report which was as follows: "Microscopic sections show slight variation in the size and shape of the hepatic cells. Finely dispersed golden pigment is noted within them. There is some lymphocytic infiltration of periportal areas but no abscesses or necrosis. No diagnosis could be made on the specimen."

Finally, in regard to therapy, the patient received a number of antibiotics as well as amebicidal drugs. None of these was beneficial. In order to facilitate our discussion it might be helpful to indicate the organs which may have been involved in the disease process, whatever its nature. In some instances the evidence of involvement is extremely limited, and although the right lung, the liver and spleen, the gastrointestinal tract, the pancreas and/or the lymphatics (in view of the findings on exploration), the heart, the genitourinary tract, including the adrenals and the brain all may be mentioned, it will not be difficult to eliminate most of them. Dr. Bercu, would you begin by discussing the possibility of cardiac involvement? Except for the history suggesting myocardial infarction several years ago there is little evidence of cardiovascular involvement. It should be stated specifically that no murmurs were heard on numerous examinations.

DR. BERNARD A. BERCU: In patients with fever of unknown origin subacute bacterial

endocarditis, either on the left or the right side of the heart, should be considered. In the absence of a murmur and of embolic phenomena I do not believe that this diagnosis merits more than passing mention.

DR. SCOTT: Would you discuss lesions of the gastrointestinal tract, Dr. Mendeloff?

DR. ALBERT I. MENDELOFF: Very little evidence points to significant gastrointestinal disease. The patient did have occult blood in the stool but it was minimal, and in view of the negative findings of exploratory laparotomy I would be inclined to dismiss the possibility of significant gastrointestinal lesions. I might say in passing that this case indicates the value of performing benzidine tests, since only on one occasion was the guaiac test also positive. On the basis of our studies we would expect only occasional guaiac tests to be positive with a 2+ benzidine test, since the latter result is obtained with extremely small quantities of blood.

DR. SCOTT: Would you eliminate the pancreas as well?

DR. MENDELOFF: Yes, I would.

DR. SCOTT: Dr. Reinhard, at operation several enlarged lymph nodes were noted in the region of the pancreas. Do you attach significance to this finding?

DR. EDWARD H. REINHARD: One certainly would have to consider the possibility of a lymphoma, perhaps Hodgkin's disease. The symptoms of weakness, fatigue and fever would be compatible with lymphoma. The only other point in favor of that diagnosis was the presence of the lower mediastinal mass, and therefore, although I do not believe that lymphoma can be excluded, I think it is unlikely.

DR. SCOTT: You followed this patient, Dr. Kenamore. Would you discuss the possibility of liver involvement.

DR. BRUCE A. KENAMORE: There were several abnormal liver function tests but an essentially negative biopsy. We were worried about the possibility of liver abscess as the cause of fever and, as has been indicated, laparotomy was performed as a desperation measure to determine whether solitary or multiple abscesses were present. It is almost inconceivable that an abscess would have been missed in view of the systematic aspiration of various areas of the liver at the time of operation.

DR. JACK BARROW: In evaluating the liver function tests it is pertinent that fever of the degree which this patient exhibited may be responsible for bromsulphthalein retention of the degree recorded here.

DR. KENAMORE: It is of interest that only one observer was able to feel the patient's spleen and he only thought that the tip was palpable. Yet at the time of laparotomy the spleen was definitely enlarged. This disparity may have been due to the fact that within the twenty-four-hour period prior to operation the patient received a large quantity of blood, enough to have produced splenic engorgement.

DR. SCOTT: Dr. Goldman, what about the genitourinary tract? Hypernephroma is always listed among the causes of fever of unknown origin.

DR. MELVIN L. GOLDMAN: In this case there is nothing to suggest the presence of a renal tumor—the pyelograms were entirely negative and at no time was there hematuria.

DR. SCOTT: Dr. Elliott pointed out that the chest x-rays revealed an infiltrate consistent with pneumonitis and has suggested that there was narrowing of the right lower lobe bronchus. I would like to ask Dr. Alfred Goldman to comment on the nature of the pulmonary disease.

DR. ALFRED GOLDMAN: The history of cough productive of mucopurulent sputum for months and x-ray changes consistent with low grade pneumonitis represent clear-cut evidence of an inflammatory process in the lungs, but whether it was primary or secondary is not clear. He could have had bronchiectasis with secondary infection, a chronic process such as lipoid pneumonia, or pneumonitis secondary to bronchial obstruction such as might be produced by bronchogenic carcinoma.

DR. SCOTT: Before we discuss the neurologic symptoms, Dr. Alexander, will you tell us whether you believe this patient had one of the collagen diseases? Fever and multiple organ involvement characterize most of this group.

DR. HARRY ALEXANDER: No, the clinical picture doesn't fit closely any of the so-called collagen disorders.

DR. SCOTT: Examination of the urine for porphobilinogen was negative, Dr. Reinhard. Does acute porphyria deserve further attention?

DR. REINHARD: No.

DR. SCOTT: The differential diagnosis in fever of unknown origin includes many infectious diseases, including those due to bacteria, parasites, fungi and viruses. Dr. Harford, would you comment on this large and important group of diseases?

DR. CARL G. HARFORD: I do not think the available evidence supports the diagnosis of any infection. Liver abscess was a reasonable possibility prior to operation, but after hearing Dr. Lischer's operative note I am willing to exclude it.

DR. SCOTT: One of the most striking features of the patient's illness was the bradycardia. The pulse rarely went above 80 or 90 per minute despite temperature elevations up to 40°C. What significance, if any, should be placed on this observation?

DR. HARFORD: Bradycardia, of course, is a classic sign in typhoid fever. It also occurs in other forms of salmonella infection, in primary atypical pneumonia, and in certain exotic infections which can be excluded here for geographic reasons. Looking over the literature I did find a statement to the effect that the fever of amebic hepatitis may be associated with a relatively slow pulse, but it is clear that the patient did not have amebic hepatitis. The mechanism of bradycardia in infection is entirely unknown. Although relative bradycardia is extremely common in typhoid fever, if typhoid vaccine is injected either into man or experimental animals the fever which results is accompanied by tachycardia. Likewise, artificial fever therapy is characterized by tachycardia. In the present case, therefore, the bradycardia, like the fever, must be considered to be of unknown origin. In passing it may be recalled that bradycardia is not an uncommon concomitant of increased intracranial pressure. Here, however, the spinal fluid pressure was normal.

DR. SCOTT: The central nervous system may have been involved in view of the patient's obtundity and the abnormal EEG. Dr. O'Leary, do you have any additional comments to make about the latter?

DR. JAMES L. O'LEARY: I can only add that the electroencephalogram was clearly an abnormal one characterized by moderate voltage four per second activity with occasional slower sequences. There was no clear focalizing tendency evident but there was a dominance of activity over the left posterior area as indicated by waves of higher amplitude. This finding, like the 2 mm. shift in the position of the pineal gland, was suggestive but by no means conclusive of a space-taking lesion. Records such as this one are seen in metabolic disorders such as porphyria, hypocalcemia or severe electrolyte imbalance, and in association with tumors of the corpus callosum. In attempting to reach a specific diagnosis, however, we receive little help from the electroencephalogram.

DR. SCOTT: Dr. Levy, could we return for a moment to the subject of bradycardia and increased intracranial pressure? Since the two are not constantly associated, will you tell us under what circumstances they are apt to occur?

DR. IRWIN LEVY: Relative bradycardia should always make one think of brain abscess, although as far I know, this concept has only an empiric basis. When I saw this patient in consultation, I was of the opinion that the central nervous system involvement was secondary rather than primary, and I was not impressed with the likelihood of a space-occupying lesion. On the other hand, in view of the electroencephalographic findings, the border-line shift in the pineal gland and the development of the right Babinski sign I suggested a small pneumoencephalogram as a means of ruling out a mass. If the patient had had an abscess in the left cerebral hemisphere, surgical intervention would have been essential. However, it was decided to explore the abdomen first and consequently the pneumoencephalogram was never performed.

DR. SCOTT: The fact that the spinal fluid pressure and the spinal fluid itself were both normal did not rule out brain tumor or abscess?

DR. LEVY: In general, one expects to find abnormalities in the spinal fluid and an increase in pressure with either one, but exceptions occur. It should be mentioned that the degree of fever which this patient had was not characteristic of brain abscess with which there is usually little or no temperature elevation.

DR. O'LEARY: The electroencephalogram was not consistent with the presence of a brain abscess. Usually the activity over an abscess is profoundly slow. Conversely, it was not inconsistent with a metastatic lesion for unless a metastasis is surrounded by edema, marked slowing is not encountered.

DR. SCOTT: Dr. Alexander, would you care to sum up the discussion?

DR. ALEXANDER: I think you have covered the possibilities very well in this extremely difficult case. Dr. Elliott's original suggestion of carcinoma of the lung with metastasis to the brain seems to me to be the most reasonable one. I believe the patient was too ill to have had a pulmonary infection alone.

DR. ROBERT J. GLASER: There was no history which suggests that the patient used oily nose



FIG. 1. The liver shows small, discrete nodules of gray tissue adjacent to portal spaces. The spleen contains smaller suet-like nodules throughout the congested parenchyma and is itself enlarged to 820 gm.

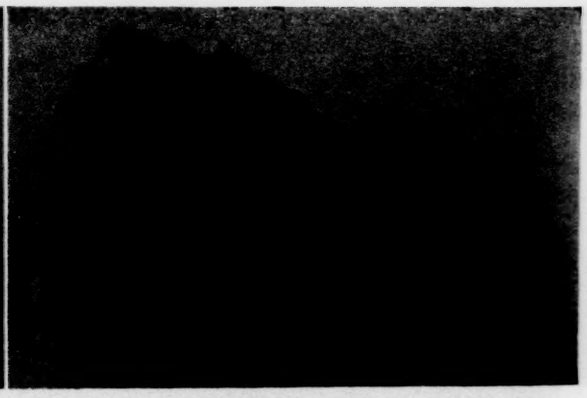


FIG. 2. The enlarged lymph nodes at the root of the mesentery and about the aorta. These nodes are adherent but discretely outlined and the parenchyma is replaced by a mottled gray tissue.

drops, but Dr. Goldman's suggestion of lipoid pneumonia is a good one. We have seen cases with a prolonged course comparable to the one this patient exhibited. A brain abscess, if present, could have been secondary to the pulmonary lesion.

DR. SCOTT: My own conclusion is that the patient probably had a bronchogenic carcinoma with either a metastasis or an abscess in the left cerebrum.

Clinical Diagnosis: Carcinoma of the lung with ? metastasis to the brain.

PATHOLOGIC DISCUSSION

DR. KYU TAIK LEE: The principal lesions were in the organs of the abdomen. The liver was enlarged to a weight of 2,240 gm. As is illustrated in Figure 1 the cut section showed a mottled pattern of moderate congestion, and there were a few discrete, spheric nodules of grayish tissue about the portal spaces. The spleen weighed 820 gm. It contained numerous small, gray, suet-like nodules throughout the soft, dark red parenchyma. The lymph nodes, particularly about the lower abdominal aorta but also those of the tracheal, bronchial, mediastinal and peripancreatic groups, were enlarged to diameters of 2 to 4 cm. The group anterior to the abdominal aorta is shown in Figure 2. These nodes were adherent to one another and moderately firm. The capsules were slightly thickened, and the individual nodes were sharply outlined. On section they were a mottled gray and slightly granular and the tissue bulged from the cut surface. A few petechiae were noted in these nodes but there was no apparent necrosis. In the bone marrow of the sternum and lumbar vertebrae there were gray, round nodules of tissue similar to that in the lymph nodes, spleen and liver.

The lungs were heavy due to an advanced degree of congestion. On palpation of the lower lobe of the right lung a few indistinct irregular foci of increased consistency were discerned and on cut section these nodules exuded pus from their surface. There were large dense hyaline thickenings of the right parietal pleura over the upper and lower lobes. These foci measured 7 by 6 cm. There was also an area of thickening and calcification 6 cm. in diameter on the right leaf of the diaphragm. The heart showed a slight degree of arteriosclerosis in the coronary arteries and small foci of fibrosis in the myocardium of the posterior septum but was otherwise not remarkable. The brain revealed no pathologic change externally or on multiple step sections. The remainder of the viscera showed no relevant pathologic alterations.

DR. DAVID E. SMITH: As Dr. Lee has presented the gross description of the organs in this case, I think the realization has occurred to all of you that this is an example of the ancient diagnostic dilemma of so-called abdominal Hodgkin's disease. The enlarged lymph nodes and spleen infiltrated with variegated tumor tissue are quite typical and the small nodules in the liver and bone marrow were consistent with this impression. The microscopic slides do little more than confirm this diagnosis.

Figure 3 is from the edge of a lymph node. It shows the variegated composition of the infiltrat-

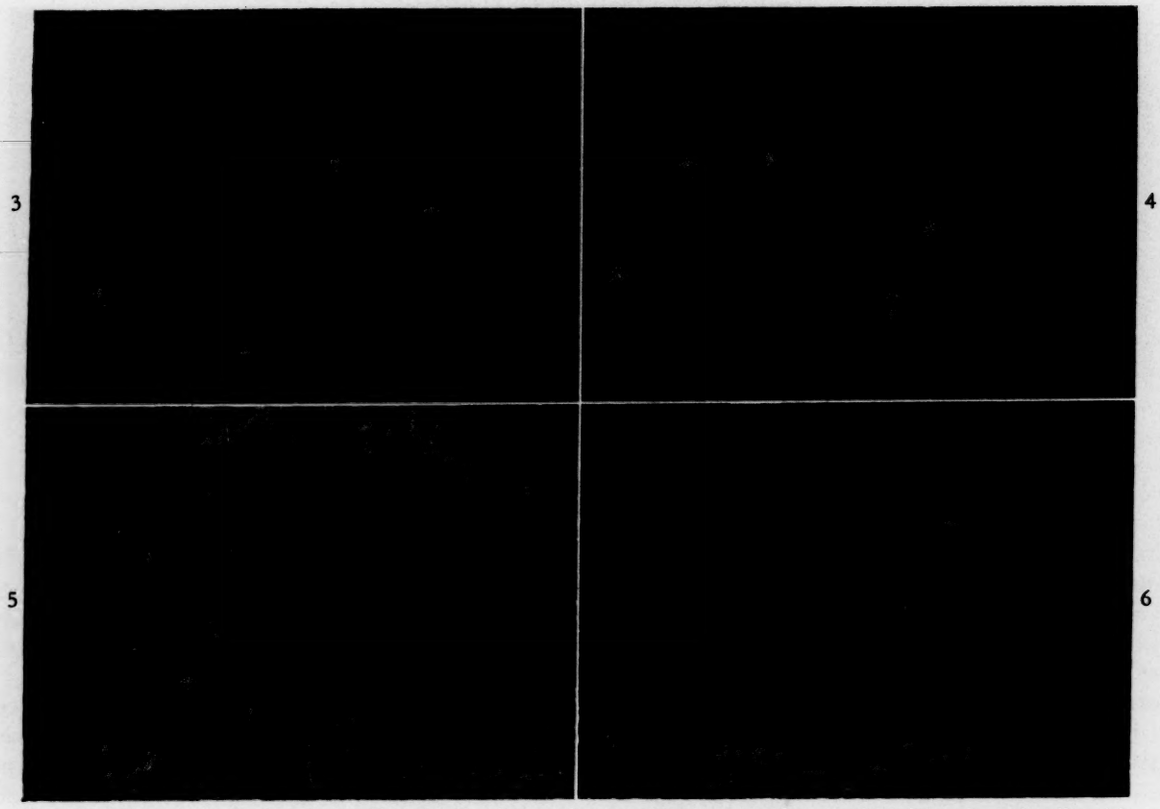


FIG. 3. A lymph node showing infiltration by large pleomorphic mononuclear and multinucleated cells with obliteration of the peripheral sinus and infiltration of the surrounding adipose tissue.

FIG. 4. A section of the liver showing Hodgkin's tissue infiltrating the portal space.

FIG. 5. A nodule of typical Hodgkin's tissue in a section of vertebral bone marrow. Similar nodules were present in sternal marrow sections.

FIG. 6. A small bronchus from the lower lobe of the right lung showing ulceration and acute inflammation in an area of bronchopneumonia.

ing cells which destroy the architecture of the node and obliterate the peripheral sinus. The large multinucleated cells of Hodgkin's disease can be discerned throughout the lower part of the illustration and smaller cells can be seen infiltrating the adipose tissue about the node. Figure 4 shows a portal space in the liver with the same type of Hodgkin's tumor tissue infiltrating the connective tissue and enlarging the portal triad. The surrounding hepatic parenchyma shows the effects of pressure atrophy and no other pathologic alteration. The spleen contained a large amount of similar tumor tissue. There was in addition congestion of the intervening splenic parenchyma, but the major part of the increased size of this organ was undoubtedly due to the tumor tissue. The bone marrow, as illustrated in Figure 5, was extensively involved. This particular section is from the vertebral marrow, but the sections of sternal marrow are equally impressive for the presence of the large nodules of Hodgkin's tissue embedded in the marrow spaces.

The final illustration (Fig. 6) is of a section from the lower lobe of the right lung. It shows a small bronchus, the wall of which is ulcerated and inflamed, with considerable cellular infiltration and deposition of fibrin. In the surrounding parenchyma of the lung there is essentially a purulent bronchopneumonia of the ordinary type. The involvement of the bronchi to this prominent extent suggests that there is an element of chronic bronchitis present which is probably more consistent with the long duration of clinical symptoms than a simple diagnosis of bronchopneumonia.

With the establishment of the diagnosis of Hodgkin's disease and the revelation of the distribution of the organs involved there remains little to be said in clinical correlation of this

case. The difficulties faced by the clinicians in the establishment of the diagnosis of abdominal Hodgkin's disease are classic. It is perhaps worth noting that the disease is manifest in sites outside the abdomen even in a case that is as puzzling as this one. The bone marrow might well have yielded a positive biopsy if the clinical indications had been recognized. Unfortunately, we did not thoroughly examine the peripheral lymph nodes. They were not grossly enlarged, but it often happens in cases such as this that a diagnosis of Hodgkin's disease can be established by biopsy of a normal-sized lymph node.

DR. SCOTT: Dr. Reinhard, I am glad that you prevailed upon me to retain the diagnosis of disease of the lymphatic system, or lymphoma. In retrospect, is there any way in which we could have made this diagnosis?

DR. REINHARD: I think it is important to emphasize that whenever an exploratory laparotomy is performed on a patient that presents the problem of fever of unknown origin and the spleen is found to be three times normal size a splenectomy is indicated. On several occasions that come to my mind the diagnosis of lymphoma has been confirmed by exploratory laparotomy and pathologic examination of an enlarged spleen when nothing else was found. This patient's condition at operation was quite precarious, but I think had there been no other contraindication to removing the spleen, the diagnosis would have been apparent.

Final Anatomic Diagnoses. Hodgkin's disease involving the tracheal, bronchial, peripancreatic and periaortic lymph nodes, spleen, liver and bone marrow of the sternum and vertebrae. Bronchopneumonia of the lower lobe of the right lung.

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Research Society Abstracts

Southern Society for Clinical Research

ABSTRACTS OF PAPERS PRESENTED AT THE SEVENTH ANNUAL MEETING, NEW ORLEANS, LOUISIANA, JANUARY 30, 1954

Molecules, Measurements and Men

Presidential Address by George T. Harrell, Professor of Medicine and Dean, College of Medicine, University of Florida, Gainesville, Florida.

This Society has always permitted its President to indulge himself in flights of philosophic fancy. It is the duty of the President of any organization to take stock of the progress it has made and to place in perspective trends as he sees them.

Why was the Southern Society for Clinical Research founded? The object of the Society as found in its Constitution is, "the encouragement of research in the various medical sciences and the establishment of a forum from which new ideas may be presented to the medical profession at large." The Constitution provides that an active member may be, "any Doctor of Medicine, Doctor of Philosophy, or Doctor of Science who has accomplished meritorious research in a branch of the medical sciences related to clinical medicine who resides within the territorial limits of the Society and who enjoys an unimpeachable reputation in his profession—provided he is not more than forty-five years of age." The Society has placed upon its active members, an obligation, "actively to continue in medical research."

What has the Society done in the accomplishment of these objectives? Its record in research in the medical sciences has been good. One needs only to review the titles of the program being presented to recognize that new scientific methods are being adapted to research and new technics are being developed. Reports of research completed indicate that advanced tools such as stable and radioactive isotopes, ultracentrifugal and electrophoretic apparatuses are being regularly used. Studies are being done on enzymes, hormones and fractionated lipoproteins. The Society is adapting old methods to present problems, such as the weighing of the body to determine its specific gravity in relation to physiologic changes, biopsy of tissue—through a needle, to be sure, plethysmographic measurement, electrocardiograms, and simple determinations of the blood pressure. These various researches embrace the basic scientific disciplines of pathology, physiology, pharmacology, bacteriology and chemistry. The research has encompassed the clinical fields of medicine, surgery, obstetrics and pediatrics. The Society is apparently well aware of its obligation to wed the basic scientific and clinical aspects of medicine and is actively making known the results to the profession at large.

But what of the presentation of new ideas? Ideas are the most powerful influences in the world. An idea may promote good, as have all the great religions of mankind. An idea may promote evil, as has been amply demonstrated in recent decades by the tyrannical ideologies. Ideas outlast, in usefulness, physical manifestations of a culture. One needs only a cursory knowledge of archeology to be convinced of that fact. Great ideas have more often come from the young rather than the aged, which probably explains why we who have reached a comfortable middle age are being forcibly retired from this Society. Young people are looking to the future and are building on the present and past. Ideas are the priceless ingredient of medical progress—not the idea for a new gadget or the collection of data on some small phase of a problem previously overlooked, but the idea with a capital "I." Giant strides are made when whole new concepts are advanced, even though experimental evidence in support is lacking or incomplete, when scattered results are synthesized into a coherent thesis or when present productive trends are projected into the future. Such papers have far too infrequently been presented here.

What can the Society do to foster the generation of ideas? A few basic facts are worth reviewing to serve as a foundation for our thinking. Clinical medicine is an art which uses scientific

tools. The tools are of varying reliability, but some of them are of high precision. Even the most accurate scientific methods must be applied to a basic biologic system which is variable. When one draws conclusions from observations on an individual member of a variable system, the degree of accuracy of the conclusions drawn no longer meets scientific criteria; the "science" has become an art. The great clinicians of the past have been recognized as artists. The oath attributed to Hippocrates pledges the fledgling physician to the practice of his art. These clinicians had a philosophic approach. Efforts through original investigations to improve the accuracy of certain aspects of the art have led to the granting of the Doctor of Philosophy degree. A solid scientific floor was placed under the artist which enabled him to keep his feet on the ground while leaving his head in the clouds.

Are we overemphasizing the role of science in the practice of clinical medicine? A detectable trend toward reduction in the quality and number of students entering medicine has been evident for several years. Fewer top students in liberal arts colleges are applying to medical schools. Into what fields are these people going who would, in the past, have been judged by academic Deans as natural candidates for medicine.

Have we oversold the scientific aspects at the expense of the art, so that medicine does not present the intellectual challenge it did just a few years ago? What type of person is needed now in medicine? He should have a superior mind and should love to study, for the practice as well as the science of medicine is a never ending process of self-education. Medicine is a profession, and a profession implies a desire to serve. A practitioner serves people; the scientist serves the practitioner as well as his own intellectual drive in his ceaseless search for truth. The data which the scientist accumulates must be accurate and must lead to valid conclusions, else he has not found the truth and his conclusions will be proved false.

The scope of knowledge in the field of medicine has grown beyond that which can be completely encompassed by single individuals. By a process of evolution a team approach to research has developed, as is shown by the authors' names on the papers presented here. Medical research teams have grown like Topsy, often to the amazement of the team as well as bystanders, but the approach has been effective. Have we attempted a true team approach to the practice of clinical medicine? The South has long been recognized as a stronghold of the rugged individualist; it has, however, produced good football teams. Society—not the doctor—has decided and has enacted into law that the physician is responsible for the care of patients. As an individual he must make decisions which involve life and death in those under his charge. He does, however, use consultants and technicians as members of his clinical team. These teams also have grown haphazardly by expedient rather than by scientific design.

Is there a fruitful field for research in the interests and aptitudes of medical personnel and the possibility of welding the varied ones into a team? Some individuals are interested in men—people; they become clinicians. Others are interested in mathematics or measurements; they may become hospital physicists or physiologists. Still others are interested in molecules; they become biochemists or pharmacologists. Yet others are interested in speech or hearing or how the mind works; they become clinical psychologists or Doctors of Philosophy in other disciplines. These doctors also want to help people and many can do the things for which they are trained, including research in their professional fields, better than can the Doctor of Medicine. Proper use of such trained personnel will spread the physician's special aptitudes more widely. When industry, business and other professions are competing for the best brains in our population, we must learn to utilize our available medical manpower according to its best interests and abilities. When this is done, everyone profits—the patient, the physician, the community, as well as the science and art of medicine.

What would happen if medical scientists reviewed their individual experiences in the development of research teams and applied them to an educational pool of those students interested in medicine or health, if one chooses a wider lay frame of reference? The common core of interest is human biology. In this pool, undetected, are potential technicians, nurses, sociologists, biochemists, psychologists and physicians, not to mention laymen who will raise the money for health care and for medical research. How can we best help members of this pool to find, through a process of self-selection with guidance, their proper niche according to their individual interests and aptitudes?

How much easier would the common ultimate objective of improvement in health of the entire community be achieved if all members of the team had the same basic orientation, the same way of thinking and could communicate with one another so that they would always be understood. The problem of a common language, in which a given word means the same thing to all people who use it, is not a simple one in science or in politics, as we have come to find out in the interpretation of the word democracy" given by politicians in different parts of the world.

Will research in the development of clinical teams benefit society? The laity and the profession are well aware that the practice of medicine is rapidly changing in character as a result of the advances made possible through scientific research. The major causes of illness in childhood no longer are acute infections; they are accidents, tumors—if leukemia and emotional disturbances may be so considered. But these illnesses are among the most frequent in the older age groups. Perhaps the term, "second childhood" is appropriate after all. Could we develop ideas which take such facts into account?

Through a team approach, utilizing all the disciplines we can bring to bear, let us seek again—*re*search—for new ideas which apply to the practice of the art of clinical medicine as we have done so successfully in the science of medicine.

EFFECT OF MARKED VARIATIONS IN AMINO ACID INTAKE ON METABOLIC RESPONSE TO CORTISONE ACETATE. *Leonard P. Eliel and Robert P. Heaney (by invitation)*. Oklahoma Medical Research Foundation, Oklahoma City, Okla.

The effects of variations in protein anabolic rate on the metabolic response to oral cortisone acetate (200 to 400 mg./day) have been studied in a patient who was fed synthetic isocaloric diets of differing amino acid content. On a zero amino acid intake, administration of cortisone resulted in only a slight increase in nitrogen excretion, averaging 0.1 gm./day. Amino acids, 50 gm./day, and cortisone were given during a subsequent period of marked positive nitrogen balance. A slight negative balance was achieved only on high doses of cortisone. With an amino acid intake of 100 gm./day, after establishing nitrogen equilibrium, cortisone resulted in a prompt negative nitrogen balance averaging 1.5 gm./day. Urinary calcium, during administration of cortisone, rose 96 and 173 mg./day, at the zero and 50 gm. amino acid levels, respectively. Pre-existent hypercalcuria confused interpretation of a rise at the 100 gm. level. Typical, reproducible effects of cortisone on K, P, Na, Cl and H_2O balances, and on circulating eosinophils were exhibited at all amino acid levels.

These results provide further confirmation of antianabolic effect of cortisone on protein metabolism. In the presence of a strong anabolic stimulus this effect may be obscured. Some metabolic effects of cortisone are manifested independently of amino acid intake.

DIABETOGENIC EFFECT OF SODIUM FLUOROACETATE IN THE RAT. *Frank L. Engel, Theodore Cole (by invitation) and Kathleen Hewson (by invitation)*. Depts. Medicine and Physiology, Duke University, Durham, N. C.

Sodium fluoroacetate (SFA) is a metabolic poison which blocks the citric acid cycle at the level of the enzyme aconitase with consequent accumulation of tissue citrate and interference with energy-yielding metabolic processes. In addition to the well known metabolic effects of this poison it has now been found that a single intraperitoneal injection of SFA (0.6 to 0.8 mg./100 gm.) will induce hyperglycemia and ketosis in fasted and pair-fed rats beginning fourteen to sixteen hours later, lasting up to sixty hours in most animals and longer in an occasional animal. Thus blood sugar and ketone levels in forty-eight-hour fasted rats were 88 $\pm$ 2.9 and 4.71 $\pm$ 0.41 mg. per cent, respectively, and in rats receiving 0.8 mg. SFA at twenty-four hours were 220 $\pm$ 24.5 and 20.91 $\pm$ 3.17, respectively. One SFA-poisoned rat died on the fourteenth day of fasting with a blood sugar of 246 mg. per cent and ketone of 31 mg. per cent. Studies are in progress to determine whether permanent diabetes can be induced by SFA and whether the diabetes is a consequence of the general metabolic poisoning effects of SFA or of specific damage to the beta cells of the pancreas.

CEREBRAL HEMODYNAMICS IN ACUTE HYPOTENSION. *Frank A. Finnerty, Jr. (by invitation), Lloyd Witken (by invitation) and Joseph F. Fazekas.* Dept. Medicine, Georgetown University Medical School and The Georgetown and George Washington Medical Services, District of Columbia City Hospital.

In an attempt to establish quantitatively the critical rate of cerebral blood flow at which

signs of cerebral hypoxia developed, forty-six patients were studied including young and old normotensives, hypertensives benign and malignant, and patients with spontaneous postural hypotension. Cerebral hypoxia was induced by lowering the arterial pressure acutely with intravenous hexamethonium and/or by head-up tilting.

Although the level of arterial pressure at which signs of cerebral hypoxia became manifest varied between 100.7 to 40.9 mm. Hg. there was a critical rate for cerebral blood flow (31.5 cc./min./100 gm. brain (S.E. 0.98) and a critical value for oxygen delivery to the brain [5 (S.E. 0.10)]. The cerebral vascular resistance fell significantly in all groups, except in the subjects with spontaneous postural hypotension and malignant hypertension. In these two groups cerebral hypoxia developed at comparatively normal levels of arterial pressure. The cerebral vascular resistance was highest in the malignant hypertensive group.

The cerebral metabolic rate did not change and the cerebral arterial-venous oxygen difference increased in all patients.

Angina and electrocardiographic changes were absent during cerebral hypoxia, which suggested that the brain was more sensitive to hypoxia than the heart.

STUDIES ON THE ABSORPTION OF AN INSOLUBLE SULFONAMIDE CONVERTED TO SOLUBLE FORM IN THE INTESTINAL TRACT. *Ray E. Flake (by invitation), John Griffin (by invitation), Edna Townsend (by invitation) and Ellard M. Yow.* Dept. Internal Medicine, Baylor University College of Medicine and the Ben Taub Infectious Disease Laboratory, Jefferson Davis Hospital, Houston Tex.

The renal complications of the absorbable sulfonamides are closely related to their solubility. It is more difficult, however, to mask the bitter taste of the soluble forms of these drugs. This is a practical problem in the administration of sulfonamides to children.

A sulfonamide compound (RO-2-6222) has been developed that is quite insoluble and tasteless in a suspension. In the small intestine it is converted and absorbed as a soluble sulfonamide (sulfisoxazole.). The present study deals with the absorption, distribution and urinary excretion of RO-2-6222 in twenty-six adults and twenty children. Peak levels following the administration of single doses were reached in four to six hours in adults and at three hours in children. Significant serum levels were detected for over twenty-four hours. When the drug was administered every four hours there was a cumulative effect for the first three or four days when maximum levels were reached. Levels in the spinal fluid reflected evidence of adequate diffusion across body membranes. The rate of excretion and rate of absorption were slower than observed with other sulfonamides. It was found that larger doses of RO-2-6222 were required to obtain comparable levels usually seen with other sulfonamides.

CLINICAL APPRAISAL OF PENTAPYRROLIDINIUM (M & B 2050) ALONE AND COMBINED WITH OTHER AGENTS IN THE TREATMENT OF HYPERTENSION. *Edward D. Freis, Edward A. Partenope (by invitation) and Lawrence S. Lilenfield (by invitation).* The Cardiovascular Research Laboratory, Georgetown University School of Medicine and the V. A. Hospital, Washington, D. C.

The clinical effects of the new ganglionic blocking agent pentapyrrolidinium (M & B 2050) were compared with hexamethonium. M & B 2050 was approximately five times more potent than hexamethonium, and the duration of the hypotensive response lasted 40 per cent longer. Considerably less tolerance developed to M & B 2050 than to hexamethonium. There was little cross-tolerance.

Only 5 per cent of an oral dose was absorbed, similar to hexamethonium. Nevertheless, the hypotensive response following oral administration was more uniform and more predictable. Various extraneous factors such as postural changes, ingestion of alcohol or a heavy meal, exercise, hot weather and salt depletion intensified the hypotensive effect of pentapyrrolidinium.

Constipation was less severe and ileus was not seen. Other side effects of ganglionic blockade were similar to hexamethonium. Contrary to previous experience with oral hexamethonium, twenty-two of twenty-seven severe hypertensives could be controlled on oral M & B 2050 without severe reactions. Dosage adjustment was critical.

An additive effect was obtained both with 1-hydrazinophthalazine and reserpine while oral neostigmine usually overcame constipation. By combining M & B 2050 with standard amounts of the above agents in tablets of three different strengths effectiveness was increased,

side effects were somewhat reduced and dosage adjustment became more standardized (thirty-two patients treated for three to five months).

INFLUENCE OF ANDROGENIC AND ESTROGENIC STEROIDS ON ULTRACENTRIFUGAL AND ELECTROPHORETIC PATTERNS OF THE SERUM ALPHA AND BETA LIPOPROTEINS AND GLOBULINS IN EUNUCHOID MALES AND POST-MENOPAUSAL FEMALES. *Robert H. Furman (by invitation), R. Palmer Howard and Loyal L. Conrad (by invitation).* Oklahoma Medical Research Foundation and the Dept. Medicine, University of Oklahoma School of Medicine, Oklahoma City, Okla.

The remarkably lower incidence of atherosclerosis is premenopausal females and eunuchs has directed our attention to the effects of gonadal steroids on lipid and lipoprotein metabolism. Katz et al. demonstrated estrogen prophylaxis against experimental chick coronary atherosclerosis, and Barr et al. found higher cholesterol concentrations in Cohn fractions I and III (beta globulins) of serum from males than in serum from females. In the female, a greater proportion of the total cholesterol was detected in the fraction containing alpha globulins.

The present study includes one acromegalic, one panhypopituitary and three eunuchoid males and four postmenopausal females. All received gonadal steroids, either singly or in combination. Lipoproteins were determined ultracentrifugally (Lewis), globulins by conventional electrophoresis and lipids by the usual technics.

Alpha-1 lipoproteins were significantly reduced (occasionally made to disappear) by androgens and increased by estrogens. Beta lipoproteins showed slight or no decrease, alpha-2 lipoproteins slight increase and chemical lipids equivocal changes with the steroid doses used. Comparison of ultracentrifuge and electrophoresis patterns suggests that these steroids influence serum lipoproteins by regulating the distribution of lipids in association with globulins, especially alpha-1 globulins.

DECREASE IN KIDNEY CHOLINESTERASE ACTIVITY AFTER ADRENALECTOMY AND REACTIVATION IN VITRO BY ADRENAL CORTEX EXTRACT AND BY CERTAIN STEROIDS. *Margaret E. Greig and M. Kathleen Carter (by invitation).* Vanderbilt Medical School, Nashville, and the Upjohn Company, Kalamazoo, Mich.

In view of the relationship between the cholinesterase activity and the permeability of various tissues to ions and other substances previously reported by us, and since it is well established that certain cortical steroids also affect ion transport, it was decided to investigate the effects of adrenalectomy on rat tissue cholinesterase activity. Of a number of tissues tested for cholinesterase activity following adrenalectomy, kidney appeared to be one of the earliest to be affected. The kidney cholinesterase activity of adrenalectomized rats on the basis of wet weight and dry weight of tissue as well as per mg. N was lower than that of control animals. Addition of adrenal cortex extract, compound F or ouabain *in vitro* to the tissue from adrenalectomized animals increased the enzyme activity. Addition of these steroids to normal rat kidney *in vitro* either had no effect or inhibited cholinesterase activity.

RELATIONSHIP OF THE MEAN CIRCULATORY FILLING PRESSURE TO CARDIAC OUTPUT. *Arthur C. Guyton, Dimitri Polizo (by invitation) and Arthur W. Lindsey (by invitation).* Dept. Physiology and Biophysics, School of Medicine, University of Mississippi, University, Miss.

The *mean circulatory filling pressure* can be measured by fibrillating the heart and pumping blood from the aorta to the right atrium in order to bring all pressures to equilibrium before vasospasm can occur. Then the heart is defibrillated by electric shock and the experiment is resumed. After massive infusion of blood into a normal dog the MCFP rises markedly, the right atrial pressure rises, and the cardiac output increases. It has been found that the cardiac output remains approximately proportional to the MCFP minus the right atrial pressure. This accords very well with the concept that cardiac output is determined mainly by the factors which cause blood to return to the heart from the peripheral circulatory system. The MCFP is in reality a measure of the mean pressure head forcing blood to return to the heart. On the other hand, the pressure in the right atrium opposes the return of blood to the heart. Consequently, the relationship found experimentally is, theoretically, that which is to be expected. Because the MCFP is a function of blood volume, this relationship helps to explain many clinical findings in heart disease associated with increased blood volume, particularly in high cardiac output failure.

EFFECT OF SUB-FEBRILE DOSES OF BACTERIAL PYROGENS ON SPLANCHNIC METABOLISM AND CARDIAC OUTPUT. *Ladd W. Hamrick, Jr. (by invitation) and Jack D. Myers.* Dept. Medicine, Duke University School of Medicine, Durham, N. C.

Bacterial pyrogens have been shown to increase hepatic blood flow (HBF) and reduce BSP excretion even when the febrile response is blocked by antipyretics. Also, cardiac output is generally elevated during the febrile response. The effects of subfebrile doses of pyrogen on splanchnic metabolism and cardiac output have not been determined however.

Eleven human subjects were studied by hepatic vein catheterization two to three and one-half hours following injection of 5 gamma of purified pyrogen (pyromen®) intravenously. The range of temperature variation was -0.3 to $+0.8$°C. Compared with a control group, there was a striking increase in HBF. Arterial-hepatic venous oxygen difference decreased moderately but significantly, but not as much as HBF increased. Accordingly, there was a significant increase in splanchnic oxygen consumption. BSP clearance was markedly impaired. ($p < 0.01$ in all instances). Splanchnic glucose production was unaffected.

Cardiac output determined by the dye dilution method in seven other subjects before and two hours following 5 gamma of pyromen intravenously remained unchanged. Temperature change varied from -0.2 to $+1.1$°C. Similarly, mixed A-V oxygen differences in the eleven catheterized patients did not vary significantly from control values.

It is concluded that the effects of subfebrile doses of bacterial pyrogens on splanchnic circulation and metabolism are due to local effects and do not reflect comparable changes in cardiac output.

EFFECT OF INTRAVENOUS TRYPSIN IN EXPERIMENTAL INTRAVASCULAR THROMBOSIS. *Eric G. Hardy (by invitation), George C. Morris, Jr. (by invitation) and Michael E. DeBakey.* Dept. Surgery, Baylor University College of Medicine, Houston, Tex.

In addition to topical application, trypsin is being employed intravenously in a variety of conditions. In particular, its intravenous administration is reported to cause intravascular thrombolysis and to have a specific "anti-inflammatory" effect. Innerfield et al. reported that their dogs tolerated doses up to 100 mg./kg. and that there were "significant but variable" lytic effects on experimental intravascular thrombi.

The purpose of our project was to determine whether significant thrombolysis could be achieved under experimental conditions roughly analogous to human deep femoral thrombosis. Segmental thrombi were established in both femoral veins in dogs, and one segment was excised as a control before administering the trypsin. Twenty-four to forty-eight hours later the remaining segment was studied.

In a series of twenty-three dogs, doses greater than 50 mg./kg. were toxic, due to shock, multiple hemorrhages and, in one case, extensive intravascular clotting. No effect on the intravenous thrombi was observed. Test clots, incubated *in vitro* for twenty-four hours with blood from trypsin-treated animals, were unaltered. An anticoagulant effect only was noted, from destruction of blood clotting factors.

Trypsin is neither effective nor safe therapy in experimental venous thrombosis.

ELECTROLYTE METABOLISM AND CARDIAC ARRHYTHMIAS DURING ACUTE PROLONGED HYPERCAPNIA. *Jerome S. Harris, W. Glenn Young, Jr. (by invitation) and Will C. Sealy.* Depts. Pediatrics, Biochemistry and Surgery, Duke University School of Medicine, Durham, N. C.

The effects of severe respiratory acidosis on plasma and tissue electrolyte composition and on the electrocardiogram were studied in rats and dogs breathing a mixture of 30 to 45 per cent carbon dioxide in oxygen for periods up to four hours. In the rat there was a marked increase in plasma potassium from a mean value of 4.63 ± 0.12 mEq./L. to 11.0 ± 0.85 mEq./L. Similar changes were noted in the dog, the blood pH falling to as low as 6.6. In dogs there was a further increase in plasma potassium content when the respiratory mixture was suddenly changed to ambient air and the blood pH rose to normal. Confirming the report of Brown and Miller, the most severe electrocardiographic abnormalities were noted during the immediate post-hypercapneic period in both species.

Analyses of the rat tissues showed an increase in potassium and water content of the heart. In contrast, the potassium, sodium and water contents of liver, muscle and kidney were not altered except in animals which died before removal from the high carbon dioxide mixture. The

liver sodium and water contents in these animals were markedly increased, presumably as a result of cardiac failure.

Electrocardiographic abnormalities ranged from increased amplitude of T waves to heart block, prolonged ventricular conduction time and ventricular fibrillation. These changes were markedly influenced by therapy with hypertonic saline and glucose. The relationship between the electrocardiographic abnormalities and the alterations in electrolytes will be discussed.

CONCERNING THE MECHANISM OF THE APEX BEAT. *Tinsley R. Harrison.* Dept. Medicine, Medical College of Alabama, Birmingham, Ala.

Although the apex beat has been known since antiquity, the mechanism of its production has remained obscure. Records have been made of the apical pulsations in relation to movements of the chest (apex cardiograms) and in relation to a fixed point in front of the body (kinetocardiograms). These tracings have been compared with simultaneously recorded electrokymograms and ballistocardiograms.

The outward thrust of the apex beat begins about 0.03 seconds before the onset of ejection and is associated with the onset of the H-I downstroke of the ballistocardiogram. Ventricular electrokymograms exhibit outward movement of the apex and often an inward movement of the base at this time. The apex beat is often diminished in patients with right ventricular hypertrophy and exaggerated in force and duration in persons with left ventricular hypertrophy. This is interpreted as indicating that the contraction of the thick muscles at the base of the left ventricle forces the thinner walled apex outward. The apex beat is, therefore, thought to represent a physiologic aneurysm of the apical portion of the left ventricle. An apical rotary twist can be seen in Prinzmetal's pictures; however, the evidence indicates that the shape change in the left ventricle is the most important factor.

ACTION OF ANESTHETIC AGENTS ON THE LOSS OF K FROM MYOCARDIAL TISSUE. *William C. Holland.* Dept. Pharmacology, Vanderbilt University School of Medicine, Nashville, Tenn.

Auricles suspended in a K-free Tyrode's medium lose approximately 1.5–1.6 mM K/kg. of tissue (wet weight) during a fifteen minute interval. Addition of acetyl choline (1×10^{-3} M) to the suspending medium increases the rate of K loss from the auricles (2.1–2.2 mM). Concentrations of magnesium chloride, pentobarbital, chloretone, procaine and cocaine causing 50 to 80 per cent reduction in the amplitude of auricular contractions decrease the rate of K loss from these preparations (1.0–1.1 mM). The decrease in K ion permeability produced by the anesthetic agents can be partially or completely prevented by addition of relatively small quantities of acetyl choline (10^{-5} M) and ATP (5×10^{-6} M) to the suspending medium.

It is postulated that the release and subsequent combination of acetyl choline with the receptor protein-cholinesterase in the surface of the cardiac cell is the process that normally accelerates ion movement across the myocardial membrane. The anesthetic agents could effectively diminish transfer of K across the cell membrane by interfering with normal functioning of the K ion accelerating mechanism either directly or indirectly.

CONSISTENCY OF URINARY GONADOTROPIN LEVELS IN CASTRATE WOMEN; TIME RELATIONSHIPS TO ESTROGEN THERAPY. *R. Palmer Howard, Corinne Keaty (by invitation), Betty Jan Jeter (by invitation) and Edward C. Reifenstein, Jr.* Oklahoma Medical Research Foundation, and the Dept. Medicine, University of Oklahoma School of Medicine, Oklahoma City, Okla.

Urinary titers of gonadotropins (FSH) were determined by the method of Klinefelter et al. in one hundred specimens from each of two castrate women. The patients received courses of equine conjugated estrogens (premarin®) orally. Ten mg. daily proved necessary for prompt and consistent reduction of gonadotropin levels.

In fifty-five of sixty assays control levels of urinary gonadotropins were $>384 < 768$ m.u./day or higher. After the effect of estrogen therapy was fully manifest, levels $>96 < 192$ m.u./day or lower were noted in forty-two of forty-six assays.

In six courses of therapy with 10 mg. daily the time required for significant reduction of gonadotropin levels was consistently between eight and fourteen days. The time required for return to pretreatment levels after cessation of therapy differed in the two patients: less than ten days on two occasions in one, eighteen to twenty-six days on two occasions in the other. Treatment with 5 mg. daily maintained the reduced gonadotropin levels.

Appreciation of the degree of consistency in gonadotropin levels, and knowledge of time relationships between initiation or cessation of therapy and these levels, are necessary for proper application of this method in determining the potency of estrogenic substances in castrate women.

RED CELL SURVIVAL STUDIED SIMULTANEOUSLY WITH N^{15}-LABELED AND SEROLOGICALLY IDENTIFIABLE ERYTHROCYTES. *G. Watson James, III, Lynn D. Abbott, Jr. (by invitation), Bo Norberg (by invitation), Steffan Birkeland (by invitation) and Everett I. Evans.* Laboratory for Clinical Investigation, Depts. Medicine and Biochemistry, and Surgical Research Laboratory, Dept. Surgery, Medical College of Virginia, Richmond, Va.

Erythrocytes were labeled with heavy nitrogen in the heme of hemoglobin by oral feeding of N^{15}-glycine to a normal adult man (Type O). When maximum "tag" was obtained, 500 ml. of his washed erythrocytes were infused into a second normal adult man (Type A) who had a 750 ml. phlebotomy immediately before the infusion. At weekly intervals hemin was isolated from the recipient's blood and analyzed for N^{15}, and correlated with the red cell disappearance determined by Ashby differential agglutination. Stercobilin was prepared from feces collected in four-day periods for 160 days and stercobilin N^{15} content determined. Blood volumes were determined by T-1824 and P^{32} technics.

The only source of N^{15} in the recipient was the infused erythrocytes. Detectable amounts of N^{15} did not appear in the plasma proteins or urinary nitrogen. Although the appearance of stercobilin N^{15} showed a striking correlation with the disappearance of hemin N^{15}, labeled stercobilin was present in the stools even after the hemin isolated from circulating erythrocytes no longer had significant N^{15} content. This suggests that labeled red cells were present in the circulation for as long as 160 days after glycine feeding. Pigment reutilization or delay in excretion are also possible explanations.

From the various data the *average life span* of the infused erythrocytes was: hemin, 113 days; stercobilin, 115 days; differential agglutination for total survival, 110 days.

CLINICAL STUDIES USING CHLORPROMAZINE AS AN ANTI-EMETIC. *Bartis Kent, Ralph Knight, George Morris and Miguel Dizon (introduced by John H. Moyer).* Depts. Medicine, Pharmacology and Surgery, Baylor University College of Medicine, Houston, Tex.

In the past there has not been a drug available which would effectively and specifically control nausea and vomiting. Chlorpromazine (10-dimethylaminopropyl)-2-chlorophenothiazine hydrochloride) (S.K.F. 2601-A) (thorazine®) appears to be such a compound, acting on the central nervous system to block the vomiting reflex. In the current study one hundred patients were selected in whom vomiting from numerous causes was a therapeutic problem and in whom the diagnosis and cause of vomiting had been established. Adults were treated with 10 mg., 25 mg. or 50 mg. doses either orally or intramuscularly, repeated at varying intervals as necessary to control vomiting. Fifty-five patients were controlled with one or a few doses of the chlorpromazine. The remaining forty-five patients received chlorpromazine for three or more days, with an average of ten days per patient. In addition, fifteen non-nauseated adult patients were given 25 mg. or 50 mg. doses of chlorpromazine for one week and were observed for any toxic reactions. Liver function studies and observations on renal clearances were also made. There was no evidence of renal or hepatic toxicity. Eighty-seven per cent of the patients treated had excellent control of the nausea and vomiting. The most common side effect noted was sedation. Other side effects noted were dizziness, dryness of the mouth, mild tachycardia and slight reduction in blood pressure. It is concluded that chlorpromazine is a very effective agent for blocking the mechanism of nausea and vomiting without serious side effects.

EFFECT OF HYDROCORTISONE AND PIROMEN IN VITRO ON LEUKOCYTES OF PATIENTS RECEIVING ACTH AND CORTISONE THERAPY. *Grace P. Kerby and John A. Barrett, Jr. (by invitation).* Dept. Medicine, Duke University School of Medicine, Durham, N. C.

This investigation was undertaken to see if a direct cellular alteration is demonstrable in humans during ACTH or cortisone therapy, persistent when the tissue is removed from homeostatic influences to an environment *in vitro*. The leukocyte was studied, cellular injury being detected and quantitated by measuring the release of lysozyme from the cell into the surrounding medium.

Leukocytes of patients receiving intravenous ACTH (20 units over eighteen hours) or oral cortisone (300 mg.) were significantly less susceptible to injury by mechanical trauma or exposure to piromen® (a bacterial polysaccharide) *in vitro* than were leukocytes from untreated patients. Maximum effect in this regard did not correlate with disappearance of eosinophils but usually required a number of days for development. Leukocytes from patients on maintenance cortisone therapy did not differ from controls in their susceptibility to injury. However, lessened susceptibility to injury could be induced in both these and control leukocytes in five hours by exposure of the cells *in vitro* to hydrocortisone (15 μg. per ml.).

A direct hormonal effect *in vitro* is thus evident. A similar alteration of leukocytes occurs more slowly *in vivo*, perhaps not due solely to adrenocorticosteroid action, and persists when the cells are removed to an environment *in vitro*.

Densitometric Measurement of Changes in Body Composition during Administration of Compounds A and F. *Laurence H. Kyle, Marcus Schaaf (by invitation), Richard J. Meyer, and Lt. Richard F. Dobbins.* Dept. Medicine, Georgetown University School of Medicine, and the Experimental Diving Unit, U. S. Navy Gun Factory, Washington, D. C.

Experimental evaluation of the concept that certain adrenal steroid hormones accelerate fat deposition in the human subject has been hampered by lack of methods for the measurement of total body fat. Previous studies have indicated the feasibility of estimating body fat by measurement of body specific gravity and the present investigation concerns the application of the densitometric technic to estimation of changes in body composition which accompany administration of compounds A and F. In addition to serial measurement of body specific gravity, conducted by underwater weighing with correction for residual lung volume, study was made of nitrogen and water balance, antipyrine space and electrolyte excretion. Treatment with compound A was associated with a slight fall in body specific gravity and significant retention of sodium and water. These changes were rapidly reversed following cessation of treatment. There was less nitrogen retention than during the pretreatment control period and approximately 1.0 kg. of fat was gained during thirty days of therapy. Much more significant decrease in specific gravity accompanied the use of compound F, with little change in nitrogen balance and fluid retention of essentially the same magnitude as that seen with compound A. Thus the lowered specific gravity was mainly the result of gain in fat, which approximated 3.5 kg. It is concluded from this study that compound A has no particular affect on body fat whereas compound F may accelerate fat deposition, even in the absence of significant increase in protein catabolism.

Assay of Prothrombin and Related Factors. *Jessica H. Lewis, J. W. Fresh (by invitation) and J. H. Ferguson (by invitation).* Dept. Physiology, University of North Carolina Medical School, Chapel Hill, N. C.

The Quick test, which is commonly used for the assay of "prothrombin" is also dependent upon the plasma concentrations of proconvertin, proaccelerin, fibrinogen and certain inhibitors. On the basis of this test 191 plasma samples from 159 patients were divided into two groups: 126 normals and 65 abnormals. The abnormal group included 4 patients with congenital hemorrhagic diseases (hypoproconvertinemia, hypoproaccelerinemia and afibrinogenemia), 12 patients receiving anticoagulant therapy and 17 patients suffering from miscellaneous acquired diseases. Prothrombin assays by the standard two-stage procedure and two new methods, which will be briefly described, gave results which correlated well, suggesting that these three tests measure prothrombin specifically. The new one-stage test is preferred because of its simplicity. Proconvertin and proaccelerin were also assayed in each plasma. Patients receiving dicumarol or tromexan were found to be deficient in both prothrombin and proconvertin. Proaccelerin was markedly diminished in one patient with a congenital hemorrhagic disorder and moderately diminished in a number of other patients suffering from miscellaneous diseases with and without associated bleeding tendencies. In conclusion, it is emphasized that the Quick test is a valuable tool in indicating deficient blood clotting but that it does not serve to differentiate the cause of the deficiency.

Right Heart Compensation during Progressive Arterial Occlusion. *Arthur W. Lindsey (by invitation), John J. Gilluly (by invitation) and Arthur C. Guyton.* Dept. Physiology and Biophysics, School of Medicine, University of Mississippi, University, Miss.

Approximately two weeks postoperatively the pulmonary artery was occluded in twenty-nine dogs by means of an encompassing loop of plastic tubing anchored to a rib near the sternum and threaded out the back chest wall. Cardiac output and mean pressures from the right ventricle, pulmonary artery, femoral artery and right auricle were recorded simultaneously and studied during varying degrees of occlusion. The right heart was found to be capable of compensating over 400 per cent before the myocardium began to fail, and a principal factor responsible for its failure was inadequate coronary blood flow due to falling systemic arterial pressure. The cardiac output, the systemic arterial pressure, and the pulmonary arterial pressure distal to the occlusion remained essentially unchanged during the period of right ventricular compensation and then decreased as the right heart failed. The right atrial pressure did not rise perceptibly until the right heart failed.

The value of cardiac reflexes in right ventricular compensation was shown by the fact that the various pressures and cardiac output remained within normal ranges much longer in normal animals than in areflex animals as the occlusion was increased.

DISTRIBUTION OF POTASSIUM AND EXCHANGEABLE RUBIDIUM IN THE ORGANS OF THE DOG, USING Rb^{86}. *W. D. Love (by invitation), R. B. Romney (by invitation) and G. E. Burch.* Dept. Medicine, Tulane University School of Medicine, New Orleans, La.

To test the usefulness of Rb^{86} as a tracer of potassium in studies of myocardial electrolyte turnover, eighteen dogs were injected intravenously with this isotope and the potassium and exchangeable rubidium content of the heart and other organs compared. Although Rb^{86} was not measured, it was possible to infer that forty-five minutes after injection of Rb^{86} the Rb^{86}/Rb^{85} ratio of the myocardium was 1.5 times that of the plasma. Analysis showed that, even in the presence of constant and equal exchange of rubidium between organ and plasma, this high ratio could have resulted from "lag" in the excretion of Rb^{86} from the heart, provided that the fractional rate of exchange of myocardial rubidium (Rb^{85}) was less than three times the fractional plasma decay rate of Rb.[86]

Most organs contained exchangeable rubidium in a higher concentration than potassium, relative to the plasma. Representative values (ratio of organ Rb^{86}/K^{39} to simultaneous plasma Rb^{86}/K^{39}) were: myocardium 1.14, skeletal muscle 1.08, liver 1.91, lung 1.48, kidney 1.53, brain 0.55, and femur 0.56. Speed of uptake of Rb^{86} in each organ was qualitatively similar to that of K^{42}, reported by others.

These results confirm the usefulness of Rb^{86} as a tracer of potassium.

ELECTROCARDIOGRAPHIC CHANGES, DISTUREED LIPID METABOLISM AND DECREASED SURVIVAL RATES OBSERVED IN RATS CHRONICALLY EATING INCREASED SODIUM CHLORIDE. *G. R. Meneely, R. G. Tucker (by invitation), W. J. Darby, C. O. T. Ball (by invitation), R. C. Kory (by invitation) and S. H. Auerbach (by invitation).* Radioisotope Unit and Research Laboratory, Thayer V. A. Hospital and the Depts. Biochemistry, Medicine, Pathology and Preventive Medicine and Public Health of Vanderbilt University School of Medicine, Nashville, Tenn.

Sustained arterial hypertension was produced in rats by feeding diets rich in NaCl. Electrocardiograms of all survivors at nineteen months showed an incidence of abnormality paralleling the degree of hypertension. Electrocardiographic abnormalities occurred most frequently among the rats on the highest salt intakes, amounting to 80 per cent of those eating 9.8 per cent NaCl. Among rats which developed severe "clinical" manifestations, disturbed lipid metabolism was evidenced by increased serum cholesterol and abnormal depositions of Sudan IV staining material in renal parenchyma, arterioles and small arteries throughout the body. A low order correlation between serum cholesterol levels and systolic blood pressure was observed. Obesity occurred in a number of the control rats and less frequently in the 2.8 and 5.6 per cent NaCl groups, but it was not seen at the higher NaCl levels. Survival rates showed statistically significant decreases depending upon the amount of salt and the duration of the regimen: (1) 21 per cent NaCl beginning at four months; (2) 14 per cent at six months; (3) 7.0 to 9.8 per cent at ten months; and (4) 2.8 to 5.6 per cent at sixteen months.

UTILIZATION OF A "SYNTHETIC" TRIGLYCERIDE PREPARATION BY WEANLING RATS. *H. C. Meng (introduced by William J. Darby).* Dept. Physiology, Vanderbilt University School of Medicine, Nashville, Tenn.

We have investigated the nutritional value of a "synthetic" triglyceride preparation composed of oleic acid, 60.0; palmitic acid, 30.0; stearic acid, 7.4; and linoleic acid, 2.6 per cent. Weanling rats, weighing 40 to 45 gm., were divided into three groups of six or twelve each. The individual groups were fed the following diets: (1) Fat-free; (2) 5 and 25 per cent "synthetic" triglyceride, and (3) 5 and 25 per cent lard (controls). Food and water were allowed *ad libitum*. The experiments were carried out for thirteen weeks. It was shown by the following criteria that the "synthetic" triglyceride was utilized: The rats fed "synthetic" triglyceride did not differ from those fed the lard diet with respect to (1) body weight gain, (2) food, water and caloric intake, (3) fecal nitrogen and (4) total body water, protein, lipid, cholesterol and iodine no. of depot fat by chemical analyses. It was also observed that the rats on the fat-free diet showed retarded growth and developed pathologic changes in the hair and skin characteristic of essential fatty acid deficiency. These animals had an increased food and water intake, increased fecal nitrogen, but no changes in the above chemical analyses on per cent of body weight basis, except that the iodine no. was reduced to 83 per cent of the controls.

The above observation that "synthetic" triglyceride supports excellent growth plus the observation that rats on a fat-free diet but with supplements of the essential fatty acids do not grow normally (Deuel et al.) confirms the previous finding in dogs (Meng) that triglyceride is an essential dietary factor.

CONTINUOUS ACTH THERAPY OF THE NEPHROTIC SYNDROME. *A. J. Merrill and Joseph Wilson* (*by invitation*). Dept. Internal Medicine, Emory University School of Medicine, Grady Memorial Hospital, Atlanta, Ga.

Twenty children from one and one-half to nine years of age have received continuous ACTH therapy. One case must be considered a complete failure since five weeks of treatment failed to modify his course in any way. Differences in his clinical picture will be discussed. All of the other nineteen are free of edema and are either free of albuminuria or their pattern of response indicates that they will become so. ACTH was discontinued from six to twelve months ago in eight patients and by current standards seven of these may be considered cured. Albuminuria without edema has recurred in the eighth on three occasions after ACTH was stopped, but this has vanished promptly with brief periods of treatment and indications are that he will eventually recover completely. Twelve patients have been essentially free of albuminuria for six months or more with the exception of the relapsing patient mentioned above. One other patient relapsed in association with an attack of chicken pox. Albuminuria disappeared after one week of treatment. ACTH was continued for five more weeks then stopped. This patient has had no albuminuria for six months. Average schedules and complications of treatment, management of relapses and problems of treatment in adults will be discussed.

DIAGNOSTIC STUDIES WITH COLLOIDAL AU^{198}. *Gould A. Andrews, Malcolm P. Tyor, Ralph M. Kniseley, Samuel W. Root and Marshall Brucer* (*introduced by Arthur C. Guyton*). Oak Ridge Institute of Nuclear Studies, Oak Ridge, Tenn.

Earlier work has shown the striking concentration of intravenously injected colloidal radioactive materials in reticulo-endothelial tissues. Autoradiographic studies and radioassays of tissues obtained at autopsy have indicated that areas of neoplasm in the liver and bone marrow are characterized by almost complete absence of the isotope and represent clearly demarcated zones of low radioactivity in a field of high radioactivity. With the availability of a method for obtaining a visual record of the distribution of gamma emitting isotopes in the body of the living patient, efforts have been made to use colloidal Au^{198} as a diagnostic method for neoplasms in the liver. After intravenous administration of the isotope it has been possible to show in general the size and configuration of the liver and, in some cases, of the spleen. Large areas of metastatic neoplasm in the liver are demonstrable because of their low concentration of the radioisotope. The method is limited by the irregular shape of the organ and the respiratory movement of the patient. The size of the lesion and its location in the liver are important in determining detectability. Up to the present only large metastases which were usually clinically obvious have been demonstrated.

EFFECTS OF INTENSIVE POISONING OF DOGS WITH BOTULINUM TOXIN—TYPE A. *George G. Armstrong* (*by invitation*), *John J. Gilluly* (*by invitation*)

and Arthur C. Guyton. Dept. Physiology and Biophysics, School of Medicine, University of Mississippi, University, Miss.

By the appropriate use of artificial respiration and fluid infusions containing sympathomimetic drugs it has been possible to maintain dogs paralyzed with botulinum toxin for many hours beyond the time death would ordinarily have occurred from respiratory paralysis. One dog was maintained for thirty hours after receiving 60,000 dog M.L.D. of toxin; others have ranged from twelve to twenty-four hours. A dose-time assay in normal dogs demonstrated that 10 dog M.L.D. were sufficient to cause death within thirty hours. It is assumed, therefore, that a dog living thirty hours after receiving 6,000 times 10 M.L.D. would be intoxicated to a degree several thousand times that necessary to cause death. Yet tests designed to quantitate sympathetic activity (spinal blockade, splanchnic stimulation, Cushing reflex elicited by elevating CSF pressure) failed to establish at any point a definite sympathetic paralysis even though the animal showed complete muscular and vagal paralysis. Other tests made to check the integrity of the central nervous system, the peripheral nerve trunks, and the circulatory system failed to produce any conclusive evidence of activity by botulinum toxin during the progression of paralysis other than confirming the previously shown site of action at skeletal and parasympathetic nerve endings.

COMPARISON OF SERUM CHOLESTEROL METHODS. *Maurice Best, Edward J. Van Loon, Joan Wathem and Alma Jean Seger (introduced by J. Murray Kinsman).* Institute of Medical Research, School of Medicine, University of Louisville, and the V. A. Hospital, Louisville, Ky.

Total serum cholesterol has been determined in 303 aliquots of serum from twenty-four normal and seventeen hypercholesteremic patients by the methods of Schoenheimer-Sperry (SS), Abell, et al. (A), Gershberg-Forbes (GF), modified Pearson et al. (P), and Zlatkis, Zak and Boyle (ZZB). The A method agreed closely with the technically more difficult method of SS. Using the A method as a point of reference the following differences were noted in sera with normal and moderately elevated cholesterol values: GF, P and ZZB were respectively greater than the reference method by 15, 35 and 90 mg. per cent. In extreme hypercholesteremic nephrotic sera and mixtures of such sera with normal sera, the absolute differences are greater but on a percentage basis yield results similar to those noted in normal sera.

Evidence suggests that by the ZZB method we are measuring cholesterol plus a non-extractable lipid and/or a protein. An alcohol-acetone extract of serum yields similar results by the SS and ZZB methods yet the ZZB method is approximately 90 mg. per cent higher if determined directly on the same serum.

ACTIVITY OF MATURE GRANULOCYTES IN LEUKEMIC BLOOD. *Abraham I. Braude, Martin Brooks and Joyce Feltes (introduced by Ernest E. Muirhead).* Depts. Internal Medicine, University of Michigan and Southwestern Medical School, University of Texas.

The abnormal appearance and number of granulocytes in various leukemias suggests that mature granulocytes might be so disturbed that leukemic patients become susceptible to infections. To determine the functional state of mature granulocytes in forty-five leukemic patients, phagocytosis was measured in two ways: (1) Suspensions of leukemic leukocytes were inoculated with opsonized type II pneumococcus and phagocytosis by individual leukemic granulocytes compared with that of normal granulocytes. (2) The antistaphylococcal action of leukemic blood was determined before and after the total granulocyte count was lowered to normal by removal of the buffy coat. This technic measured the collective action of leukocytes.

The results disclosed a defect in mature neutrophils in chronic granulocytic leukemia characterized by reduced phagocytic activity of individual cells. However, the enormous increase in total number of neutrophils in peripheral blood compensated for impaired phagocytosis of individual cells so that net antibacterial activity of blood in granulocytic leukemia was equal to or greater than normal. By contrast, in chronic lymphocytic and certain acute leukemias, individual function of granulocytes was usually undisturbed but reduced numbers weakened antibacterial defense. It was possible to correlate the occurrence of infection in forty-five patients with the net antibacterial activity of the patient's blood.

A SENSITIVE VENOUS OCCLUSIVE PNEUMOPLETHYSMOGRAPHIC METHOD FOR THE MEASURE-

MENT SIMULTANEOUSLY DURING A SINGLE PULSE CYCLE OF THE TIME COURSE OF THE RATE AND VOLUME OF DIGITAL BLOOD FLOW INTO AND OUT OF THE INTACT FINGER OF MAN. *G. E. Burch.* Dept. Medicine, Tulane University School of Medicine, New Orleans, La.

Measurements were obtained with a digital pneumoplethysmograph sensitive to 0.1 cu. mm. and an electronically controlled system which permitted occlusion pneumatically of venous outflow at any preselected moment during a pulse cycle for any preselected duration. Simultaneous recordings were made mainly on second (2RF) and third right finger tips (3RF), rate (cu. mm./5 cc. part/sec.) and volume (cu. mm./5 cc. part) being recorded for 2RF. From simultaneous recording of inflow (I) and volume pulse wave for an adjacent digit, difference (D) with time between volume inflow and outflow, volume-time course of digital outflow (O) was obtained by: $O = I - D$. Mean volume flow per pulse cycle was obtained easily from volume-time curves. Time courses of first derivatives of foregoing three volume-time curves were plotted to obtain three simultaneous time course curves of *rates* of flow during a pulse cycle.

These simultaneously recorded curves permit observations of important temporal relationships between inflow and outflow, aiding in localizing certain peripheral vascular phenomena to arterial, venous or intermediate digital vessels, e.g., evidence of increased digital venous tone in chronic congestive failure. Detailed simultaneous volume and rate curves of inflow and outflow for a pulse cycle opens a new approach to study of vascular phenomena in isolated parts of intact animals, including man.

DIFFERENTIAL COUNTING OF I^{131} AND CR^{51} IN SINGLE SAMPLES OF WHOLE BLOOD. *Walter H. Cargill, Ann Payne (by invitation) and Arthur F. Dratz (by invitation).* Radioisotope Unit, Veterans Administration Hospital, Atlanta, Ga.

By using a pulse height discriminator in conjunction with the usual scintillation counting equipment it is possible to measure separately the concentrations of I^{131} and Cr^{51} in a sample of whole blood containing both radioisotopes, since the different gamma radiation spectra permit calculation of the contribution of each to the total counting rate of the mixture. If known amounts of I^{131}-labelled serum albumin and Cr^{51}-labelled erythrocytes are injected intravenously, the volume of distribution of each can be determined by counting a single sample of whole blood in a well-type scintillation crystal without separation of plasma and erythrocytes or special counting technics (differential absorption by suitable shields, allowance for decay of short-lived isotopes, etc.) which have been employed in previous attempts to measure simultaneously plasma and red cell volumes using radioisotopes. Fifteen comparisons of the ratio Erythrocyte volume/Total Blood volume determined in this manner with the hematocrit readings of the same sample have been made in four subjects under basal conditions and after the infusion of 6 per cent dextran solution or whole blood. Occasional marked discrepancies between the two measurements were noted. Changes in the "specific activity" or erythrocyte samples (counts/min. of Cr^{51} per ml. packed erythrocytes) indicate the possibility of transfers of unlabelled erythrocytes in and out of the circulation which cannot be detected by hematocrit determination.

EFFECT OF CHEMOTHERAPY ON TISSUE METABOLISM OF TUBERCULOUS GUINEA PIGS. *C. D. Cooper (by invitation), S. N. Chaudhuri (by invitation), R. Green (by invitation) and S. P. Martin.* Dept. Medicine, Duke University School of Medicine, Durham, N. C.

This laboratory has shown alterations in soluble thiol and succinic dehydrogenase in animals infected with M. tuberculosis which correlated with the degree of infection. The effect of therapy on these alterations was studied in order to relate the metabolic and chemotherapeutic response. Renal tissues were used because they reflected the general metabolic response to this disease. Thiols were determined by ampereometric titration and dehydrogenase by a quantitative tetrazolium technic. Guinea pigs were treated with isonicotinic acid hydrazide (INH) and streptomycin.

Infection produced a marked increase in soluble thiol content with diminution in succinic dehydrogenase. Therapy did not alter the degree or direction of change in soluble thiols. Streptomycin depressed the thiol content in normal tissue, thus the level in infection was within normal range. Infected animals tolerated larger quantities of streptomycin. INH tended to return the dehydrogenase level of infected tissue toward normal.

Alterations in dehydrogenase and thiols may

have an important role in changes in energy metabolism during infection. INH improved dehydrogenase activity to a greater degree than streptomycin and was associated with greater symptomatic improvement. These data emphasize the role of dehydrogenase activity in infection, therapy and symptomatology.

FURTHER STUDIES IN OBESITY IN THE MOUSE: DIETARY DILUTION STUDIES AND L-THYROXINE ADMINISTRATION IN MICE WITH GOLD THIOGLUCOSE-INDUCED OBESITY; DIETARY DILUTION STUDIES IN MICE WITH THE HEREDITARY OBESITY DIABETES SYNDROME. *K. R. Crispell, William Parson and James L. Camp, III.* Dept. Internal Medicine, University of Virginia, Charlottesville, Va.

Previous studies have shown that mice with gold thioglucose-induced obesity "in a plateau phase" make a poor adjustment to 50 per cent dietary dilution with kaolin. They fail to have a prompt increase in the volume ingested and do not maintain their weight, as do control mice. The present studies show the same inadequate response to dietary dilution during the "ascending phase" of the obesity. In contrast, mice with the hereditary obesity diabetes syndrome do not show a significant abnormality in responding to dietary dilution during the "ascending" or "plateau phase."

Daily injections of L-thyroxine in control mice result in increased food ingestion and maintenance of weight. The gold thioglucose obese mice do not increase their food intake adequately and lose weight when treated similarly.

These studies may be interpreted to indicate that gold thioglucose obesity in mice is associated with a defect in the homeostatic "hunger drive" mechanism as well as the obesity-producing defect in the "satiety mechanism." The pathogenesis of the hereditary obesity in mice has been attributed to a "primary metabolic defect" by Mayer. The present studies support this concept.

PHYSIOLOGY OF CHEYNE-STOKES BREATHING. *Jack W. Crowell (by invitation), George G. Armstrong (by invitation) and Arthur C. Guyton.* Dept. Physiology and Biophysics, School of Medicine, University of Mississippi, University, Miss.

The necessary conditions for oscillations to occur are (1) a negative reflex and (2) a time delay. These principles have been applied in the study of periodic breathing (Cheyne-Stokes) in order to find its physiologic cause. Breathing is largely controlled by the action of carbon dioxide on the respiratory center; however, there is a time delay before the blood leaving the lungs reaches the respiratory center. When the animal is allowed to rebreathe air until definitely hypercapneic and then allowed to breathe normal air, the respirations follow a damped oscillatory pattern gradually returning to normal. Experimentation in which the blood reaching the respiratory center is delayed by allowing it to flow through a long tube reveals that the periodicity of periodic breathing can be altered proportional to the time delay. With proper levels of sodium pentobarbital anesthesia, periodic breathing can be produced even without an external delay circuit, indicating that a certain center or centers must be blocked before this periodic mechanism can be released. This indicates the presence of a damping center or mechanism which under normal conditions inhibits periodic breathing.

DIFFERENCE IN DYNAMICS OF VENTRICULAR CONTRACTION AND RELAXATION IN PATIENTS WITH MITRAL STENOSIS AND INSUFFICIENCY AS STUDIED BY THE KINETOCARDIOGRAM. *E. E. Eddleman, Jr. and Robert H. Yoe (introduced by Tinsley R. Harrison).* Dept. of Medicine, Medical College of Alabama, Birmingham, Ala.

Kinetocardiograms (precordial movements) were recorded with a bellow's pick-up device in patients who were judged clinically or at operation to have either mitral stenosis or insufficiency. Simultaneous direct ballistocardiograms, carotid pulses and electrocardiograms were obtained. The kinetocardiograms from the patients with mitral stenosis were characterized by: (1) an early abnormally marked outward movement of the lower parasternal region of the chest which began about 0.04 seconds after the QRS complex and was sustained during systole, (2) a large inward movement in the same region of the chest which began late in systole and proceeded into isometric relaxation. The records from patients with mitral insufficiency are characterized by a well marked inward movement of the precordium during early ejection followed by a large outward movement just preceding isometric relaxation.

The above findings are interpreted as indicating an exaggerated anterior and rightward swing of the heart during ejection in patients

with mitral stenosis, in contrast to a late systolic anterior swing in mitral insufficiency. Thus there appear to be fundamental differences between the movements of the heart in patients with mitral stenosis as compared to those with mitral insufficiency. This may be of help in evaluating patients preoperatively for mitral commissurotomy.

GEOGRAPHY AND SARCOIDOSIS. *Max Michael, Jr., Harold M. Nitowsky (by invitation) and John T. Gentry (by invitation).* Medical Service, V. A. Hospital, Dept. Medicine, Emory University School of Medicine, and the Communicable Disease Center, U. S. P. H. S., Atlanta, Ga.

As part of a systematic study of the 300 cases of sarcoidosis detected among service men of World War II, an epidemiologic survey has been undertaken. Detailed data as to birthplace, residences, occupations, animal contacts, etc., have been obtained from most patients. In addition, the flora, fauna and geologic patterns of the environs of this group have been reviewed. The data obtained to date have been analyzed and have revealed several pertinent facts. The higher attack rates in patients whose birthplace or lifetime residence was in the southeastern United States as compared with those from other regions of this country suggests the existence of localizing factors in this "hyperendemic area." Furthermore, a concentration of cases along the coastal plain area was noted. Within this region there are significantly higher rates among service men from rural areas. No common denominators other than associations with certain soil types have been detected. The predilection of sarcoidosis for the Negro, which has been further substantiated in this study, does not account for this southeastern coastal plain, rural distribution of cases.

It is believed that these epidemiologic data must be reckoned with in considering any etiologic and pathogenic concepts of sarcoidosis.

COMPARATIVE EFFECTS OF EPINEPHRINE, NOREPINEPHRINE AND INSULIN HYPOGLYCEMIA; INFLUENCE OF AUTONOMIC BLOCKING AGENTS. *R. J. DiSalve (by invitation), Robert W. Ferguson (by invitation), Albert A. Brust (by invitation), Walter L. Bloom and Eugene B. Ferris, Jr.* Dept. Medicine, Emory University School of Medicine, Grady Memorial Hospital, Atlanta, Ga.

A comparison of certain circulatory and metabolic effects of L-epinephrine and L-norepinephrine has been made in eight human subjects. Continuous intravenous infusion for fifty minutes of 0.085 μg./kg./min. of epinephrine produced widened pulse pressure, T wave depression and increase in blood glucose and lactic acid. Double this dose caused no further significant rise in glucose but accentuated the lactic acid response significantly (p. .05). Lactic acid rise was not prevented by 100 mg. of hexamethonium intravenously before epinephrine infusion. TEAC likewise had no effect.

Nor-epinephrine (0.085 μg./kg./min.) produced bradycardia, rise in systolic and diastolic blood pressure and mild hyperglycemia, but lactic acid levels were unaffected.

Circulatory and lactic acid changes similar to those obtained with epinephrine were noted in five fasted patients during insulin hypoglycemia. Blood glucose rose spontaneously after reaching its lowest level. In the same patients insulin hypoglycemia was again induced following intravenous administration of 100 mg. of hexamethonium. Significant rise in lactic acid did not occur and spontaneous recovery of blood glucose was abolished.

It is concluded (1) L-epinephrine and L-norepinephrine differ in circulatory and metabolic effects; (2) blood lactic acid is a sensitive and perhaps quantitative indicator of epinephrine activity; (3) circulatory and metabolic effects of insulin hypoglycemia are similar to those induced by epinephrine, and appear to be due to increased secretion of epinephrine; (4) hexamethonium inhibits the release of epinephrine from the adrenal medulla during hypoglycemia.

INFLUENCE OF BODY FAT CONTENT ON BASAL METABOLISM AND METABOLIC COST OF WORK. *A. T. Miller, Jr.* Dept. Physiology, University of North Carolina Medical School, Chapel Hill, N. C.

Basal oxygen consumption, body fat content and lean body mass (LBM) were determined in forty-eight healthy male subjects. Over the range 40 to 91 kg. LBM, basal oxygen consumption per kg. LBM was independent of fat content (ml. O_2/min. = 17.35 $LBM^{0.64}$, S.E. of exponent = 0.03). This suggests that basal oxygen consumption, like water content, is a basic constant of the lean body mass.

Metabolic cost of standard work (treadmill, 15 minutes, 5 m.p.h., 10 per cent grade) was studied in sixteen subjects varying widely in fat

content. With increasing fat content there was a significant increase in the ratio of exercise to resting metabolism (r = 0.68) and in the O_2 consumption per kg. LBM (r = 0.59). Increasing weight also increased the ratio of exercise to resting metabolism (r = 0.61) because of the high correlation between weight and fat content. If the influence of fat content is eliminated (method of partial correlations), the influence of weight *per se* on the ratio of exercise to resting metabolism and on the exercise metabolism per kg. LBM is reduced to insignificance (r = 0.15).

TREATMENT OF HYPERTENSION WITH RAUWOLFIA SERPENTINA ALONE AND IN COMBINATION WITH HEXAMETHONIUM OR HYDRALAZINE. *John H. Moyer and W. E. Livesay* (*by invitation*). Depts. Pharmacology and Medicine, Baylor University College of Medicine, Houston, Tex.

A group of 150 patients with all grades of severity of hypertension have been studied on an ambulatory outpatient basis. All patients had an average control blood pressure of not less than 160 systolic and 110 diastolic. Fifty-three per cent of the patients treated with rauwolfia (rauwiloid®) alone responded with a fall in mean blood pressure of 20 mm. or more and 22 per cent of these became normotensive with a fall in mean blood pressure to 110 mm. Hg or less. More severe cases and patients with complications due to hypertension were found to be far less responsive than the milder uncomplicated cases. Side effects were all benign. When hydralazine® was added to eleven patients who were unresponsive to rauwolfia serpentina alone, eight became responsive. All but three of thirty-nine patients responded to combined therapy with hexamethonium and Rauwolfia serpentina and nineteen of the responding patients became normotensive. Retinopathy was found to be uniformly reversible in eleven cases with malignant hypertension in this group. It was concluded that Rauwolfia serpentina is an effective hypotensive agent in mild uncomplicated hypertension. When hydralazine is given in addition to rauwolfia to this group of patients who do not respond to rauwolfia alone, a significant reduction in blood pressure is frequently observed. A combination of hexamethonium and rauwolfia can be expected to control the majority of severe complicated cases of hypertension.

SODIUM AND POTASSIUM EXCHANGES ASSOCIATED WITH NOR-EPINEPHRINE INFUSIONS. *E. E. Muirhead, A. Goth, and F. Jones* (*by invitation*). Depts. Pathology and Pharmacology, Southwestern Medical School of the University of Texas, Dallas, Tex.

Previous studies in this laboratory have suggested that total extracellular sodium decreases while potassium tends to increase in the hypertensive nephrectomized dog. This study was done to determine the relationships which may exist between vasoconstriction and the movement of electrolytes.

Nor-epinephrine was given by intravenous infusion to seven dogs under pentobarbital anesthesia. Markedly elevated blood pressures were maintained for thirty to fifty minutes. Total dosage varied from 2 to 7 mg. per kg. Sodium and potassium were determined on arterial blood samples. ECF volume was estimated by the radioactive sulfate method in four of the dogs.

RESULTS

Dog	Sodium	Potassium
	Maximal change in mEq./L.	
1	− 6	+2.0
2	−17	+4.0
3	−24	+3.5
4	−23	+4.0
5	−14	+3.0
6	−10	+1.0
7	− 1	+1.5

The fall in serum sodium occurred immediately following the blood pressure rise. Potassium elevation was delayed. Participation of arteries in the uptake of sodium is likely in view of the rapid and powerful effect of nor-epinephrine on these structures.

HEMODYNAMICS OF ACUTE HYPERTENSION PRODUCED BY STIMULATION OF THE CEREBRAL CORTEX. *J. L. Patterson, Jr., H. G. Langford* (*by invitation*), *R. R. Porter, M. Bernhaut* (*by invitation*), *E. Sharpe* (*by invitation*), *L. Rennie* (*by invitation*) *and E. C. Hoff* (*by invitation*). Depts. Medicine and Neurological Science, Medical College of Virginia, Richmond, Va.

Electrical stimulation of appropriate areas of the cerebral cortex produces a prompt pressor response in the lightly anesthetized animal. The present studies explored the hemodynamic mechanisms of this phenomenon.

Observations to date have been made during fifty stimulations in eleven dogs. Right atrial, pulmonary arterial and pulmonary "capillary" pressures were recorded. Cardiac output was determined by pressure-pulse contour analysis.

Ten-second stimulation of motor or premotor areas produced an abrupt rise in mean aortic pressure averaging 62 mm. Hg (55 per cent), with little change or slight increase in cardiac index. Calculated vascular resistance usually increased, in some cases markedly. Pulse rate was affected very little or was moderately increased. Pulmonary capillary, pulmonary arterial and right atrial pressures were unchanged or increased slightly. Alternate stimulation of right and left cortex for 90 to 180 seconds produced similar findings, except for more marked and sustained systemic hypertension.

It is concluded that the primary change was systemic vasoconstriction. The hypertension produced differs from that caused in both the greater and lesser circuits by intracisternal fibrin, but suggests certain analogies to essential hypertension in man. One factor in the maintenance of cardiac output with rapidly rising vascular resistance may have been an effect of cardiac innervation upon ventricular contractility.

CHEMISTRY AND PHARMACOLOGY OF 1-HYDRAZINOPHTHALAZINE. *H. Mitchell Perry, Jr. (by invitation) and Henry A. Schroeder.* Hypertension Division, Dept. Internal Medicine, Washington University School of Medicine, St. Louis, Mo.

1-Hydrazinophthalazine (apresoline®) is an essential drug in the management of severe and malignant hypertension, for which no effective substitute has been found. The highly reactive hydrazine moiety combines with carbonyl groups. In the human body no evidence of depression of blood pyruvate or total carbonyl was demonstrated in patients taking large doses (up to 800 mg. per day), Urinary excretion never exceeded 3 per cent of orally or parenterally administered drug, of which a variable fraction was bound to sulfhydryl. The fate of the remainder is unknown. The ratio of bound to free diminished as the blood pressure fell. When BAL was given, all was in the bound state.

Substituted hydrazine also combines with some heavy metals, such as iron, copper, cobalt, manganese and molybdenum. Studies are in process to determine their rates of excretion. The mild anemia frequently seen may be due in part to this reaction.

In rats the pressor actions of naturally occurring catecholic and aliphatic amines were inhibited only by very large doses (60–80 mg. per kg.), possibly a non-specific effect. The pressor action of indolic amines was enhanced. Only pervanadate and pherentasin were inactivated by small amounts.

Most agents acting in renal hypertensive rats have an affinity for metals (BAL and other aliphatic mercaptans, pyrophosphates, thiocyanates). Various ethylene diamine tetraacetates showed similar hypotensive effects. A possible action of substituted hydrazines may lie in an affinity for a heavy metal concerned in contraction of vascular smooth muscle.

CHANGES IN LUNG COMPLIANCE ASSOCIATED WITH PULMONARY VASCULAR CHANGES. *W. W. Pryor and E. B. Page (introduced by J. B. Hickam).* Dept. Medicine, Duke University School of Medicine, Durham, N. C.

Increased stiffness, or decreased compliance, of the lungs occurs in some cardiovascular disorders, notably mitral stenosis. The present work is concerned with the mechanism of this change, especially the relation between increased pulmonary vascular pressure and decreased pulmonary compliance.

Pulmonary compliance has been measured in patients with mitral stenosis who have also had measurements of pulmonary vascular pressures at rest and exercise. Many mitral patients with a moderately reduced resting compliance have a considerable drop in compliance during exercise. Under similar conditions normal subjects do not show such changes. However, rapid infusion of a large quantity of albumin solution into normal subjects or the sudden release of venous thigh tourniquets will markedly reduce pulmonary compliance for a short time. These results suggest that increasing pulmonary vascular pressures will reduce compliance. Conversely, it would appear that changes in compliance under controlled circumstances may be a useful index of changes in pulmonary blood volume.

Subjects with severe mitral stenosis and markedly reduced compliance at rest do not show much compliance change on exercise. It seems probable that lung stiffness in these subjects is primarily due to changes in the lung parenchyma rather than to increased vascular pressure.

SYMPATHO-ADRENAL SURGERY IN THE MALIGNANT PHASE OF ESSENTIAL HYPERTENSION. *Samuel T. R. Revell, Jr., Francis J. Borges, George H. Yeager, James G. Arnold, Jr. and Richard E. Alquist, Jr.* (*introduced by Theodore E. Woodward*). Depts. Medicine, Surgery and Neurological Surgery, School of Medicine, University of Maryland, Baltimore, Md.

To appraise accurately sympatho-adrenal surgery, it was decided patients would be limited to those in the malignant phase of essential hypertension. This was defined as the rapidly progressive hypertensive state exhibiting papilledema and hemorrhagic exudates in which no primary etiology of hypertension was demonstrable. Thirteen of seventeen patients fulfilling these criteria exhibited a BUN of over 40 mg. per cent.

The management of these patients fell into three groups: (1) Combined procedures (sympathectomy and adrenalectomy): One patient died four days after first stage, five patients are alive two to twenty-nine months after operation. (2) Adrenalectomy alone: Four died in the immediate postoperative period, one died forty-eight days postoperatively of bleeding ulcer and uremia. (3) No definitive procedure: Six died before completing studies.

Adequate material for pathologic study was available from thirteen patients; necrotizing arteriolitis was demonstrable in twelve.

No beneficial results were observed following adrenalectomy alone. The five living patients had bilateral total adrenalectomies and sympathectomies: one followed twenty-nine months is well including uncomplicated pregnancy twenty-six months postoperatively; one followed fourteen months has no hypertensive residual; two followed for too short a period to evaluate; one followed seven months is definitely improved.

The results obtained with bilateral total adrenalectomies and sympathectomies justify further investigation.

POST-PRANDIAL DECLINE IN T WAVE. *I. Rochlin and Patricia F. Norman* (*introduced by Tinsley R. Harrison*). Dept. Medicine, Medical College of Alabama, Birmingham, Ala.

In four patients recently observed a diagnosis of coronary artery disease had been made largely on the basis of differences observed at different times in T waves from the same lead. It was found that in these four subjects the differences could be induced at will following a large carbohydrate meal and prevented by simultaneous administration of potassium chloride with the meal. Subsequent studies in six normals have shown T wave lowering but no inversion in several leads under the same circumstances.

MECHANISMS OF DIAMOX (ACETAZOLEAMIDE) DIURESIS. *Arthur Ruskin, Neal Reznikov and Belle Ruskin* (*introduced by Raymond Gregory*). Dept. Internal Medicine, University of Texas Medical Branch, Galveston, Tex.

The carbonic anhydrase inhibitor diamox® was found to be an effective diuretic (50 to 600 per cent twenty-four-hour urinary output increase) in twenty-three of thirty-three cases of congestive heart failure, including three mercurial-fast patients. On a 500 mg. sodium diet the excretion of water, sodium and potassium was promoted about equally by 500 mg. of diamox administered once daily or in four such doses per day.

The diuresis, natriuresis and rise in urinary pH were usually evident in all eight hourly specimens and for many days, indicating perhaps more rapid changes of carbonic anhydrase activity or otherwise more prolonged depression of tubular reabsorption than in normal dogs. Preliminary experiments in rats indicate slight depression of renal succinic dehydrogenase activity by diamox. This finding, together with often significant rises in urinary chloride excretion in heart failure (versus normals), may indicate other pathways of decreased tubular reabsorption than simple carbonic anhydrase inhibition. Hemodynamic mechanisms are apparently absent.

HEXAMETHONIUM CHLORIDE AND 1-HYDRAZINOPHTHALAZINE (HYPHEX) IN MALIGNANT HYPERTENSION. *Henry A. Schroeder and H. Mitchell Perry, Jr.* (*by invitation*). Hypertension Division, Dept. Internal Medicine, Washington University School of Medicine, St. Louis, Mo.

The surviving members of one hundred patients exhibiting malignant hypertension of all grades of severity were treated with oral hexamethonium chloride and 1-hydrazinophthalazine (hyphex®) for seven to twenty-eight months. The results have been superior to other forms of therapy. Of forty-eight with nitrogen retention, five initially uremic individuals died without improvement and two others developed progressive renal failure. Eight deaths from causes unrelated to hypertension include four

from interstitial pneumonia. Cessation of one or both drugs was followed by death within a month in all of nine. The remaining twenty-four are asymptomatic without progression of renal failure.

Of fifty-two without renal insufficiency six have died, one from cerebral arterial thrombosis and five from non-hypertensive causes. The remaining forty-six are without fundal changes or progression of the secondary effects of hypertension. Cessation of one drug has resulted in two deaths, and of both for all of eight. Temporary discontinuation was rapidly followed by return of hypertension.

The occurrence of reversible collagen disease resulting from 1-hydrazinophthalazine has caused a serious therapeutic problem in five when the drug was discontinued, good control of blood pressure being unobtainable with increased doses of hexamethonium, Rauwolfia serpentina and protoveratrine. A therapeutic substitute for 1-hydrazinophthalazine is essential for continued management.

EMOTIONAL TENSION AND EXCRETION OF CORTICOIDS AND CREATININE. *Theodore B. Schwartz and Daniel R. Shields (by invitation)*. Dept. Medicine, Duke University School of Medicine, Durham, N. C.

The relation between emotionally stressful situations and the urinary excretion of "adrenal corticoids," measured as beta-glucuronidase-hydrolyzed formaldehydogenic steroids (GFS), has been explored. As a possible index of muscle tension, urinary creatinine was also determined. Emotional stress was estimated simply as a subjective evaluation of low, medium or high "tension." Data were obtained from twenty-three medical students during three consecutive two-hour periods before, during and after a final written examination in medicine. Prior control observations were made on twelve of these students by subjecting them to the entire procedure except that two hours of lectures were substituted for the actual examination. It was found that GFS, but not creatinine, excretion was positively correlated with tension estimates. During the two-hour examination period both GFS and creatinine excretions rose significantly above pre-examination levels. Control determinations of GFS excretion tended to show a similar increase but to a significantly lesser degree.

These results cannot be interpreted beyond the limits of the experimental situation since, under other circumstances, seemingly contradictory observations of equal statistical validity may be made. An example is the significant *negative* correlation between serial daily tension estimates and GFS excretion in a single "normal" individual subjected only to stresses of everyday existence.

GROWTH HORMONE CONTENT OF HUMAN PLASMA. *Albert Segaloff and Eugene L. Komrad (by invitation)*. Endocrine Research Laboratory, Alton Ochsner Medical Foundation, and the Tulane University School of Medicine, New Orleans, La.

The response of the tibial cartilaginous plate in hypophysectomized immature male rats has been employed as a measure of growth hormone. We have followed the standard injection period of four days with sacrifice of the animals on the fifth day and measurement after staining with silver nitrate.

Studies were done on plasma alone and plasma with added beef hypophyseal growth hormone. The curves obtained with growth hormone added to plasma have shown that these curves parallel those obtained with either growth hormone dissolved in saline or bovine albumin. The distance between these parallel lines has been interpreted as being due to the growth hormone contained in the plasma. Some plasmas have then been assayed by measurement directly against growth hormone standard curves.

With this method we have found detectable amounts of growth hormone in the majority of plasmas which have been studied. In general, adults appear to have more growth hormone in their plasma than children. So far both of our own patients with active acromegaly have had plasma growth hormone values higher than any control studied to date. The three untreated patients with panhypopituitarism gave negative assays for plasma growth hormone.

Although patients with other conditions have been studied, there are too few assays in each condition as yet to establish definite trends.

NATURE OF HYPOCHLOREMIC ALKALOSIS INDUCED BY ADRENAL STEROIDS. *Donald W. Seldin, Floyd Rector, Norman Carter and John Copenhaver (introduced by Ernest E. Muirhead)*. Depts. Internal Medicine and Pharmacology, Southwestern Medical School, University of Texas, Dallas, Tex.

Alkalosis induced by adrenal steroids and sodium results either from accelerated urinary acid excretion or transport of acid into cells. To characterize the alkalotic process, rats were given DCA and a high sodium, potassium-free diet. Control rats received a diet containing sodium and potassium, but no DCA. Urines were analyzed for acid excretion (ammonium and titratable acid), and kidneys from both groups were analyzed for glutaminase, glycine oxidase, L-amino acid oxidase and D-amino acid oxidase, using tissue slice and tissue homogenate technics.

Acid excretion was uniformly higher in experimental than in control animals. Paralleling the increased acid excretion, glutaminase activity in experimental animals was 1892 ± 445 μM NH_3/100 mg. dry tissue/hour as compared to 656 ± 102 μM NH_3/100 mg. dry tissue/hour in control animals. No differences were observed in activities of glycine oxidase, L-amino acid oxidase or D-amino acid oxidase; however, these activities were determined only by tissue slice technics.

These findings suggest that hypochloremic alkalosis resulting from DCA and sodium is the consequence principally of the renal loss of acid, largely as ammonium. Accelerated ammonium secretion apparently results from increased renal glutaminase activity. This adaptation of glutaminase may be stimulated either by potassium depletion or intracellular acidosis.

CLINICAL AND MORPHOLOGIC FINDINGS IN RENAL NEEDLE BIOPSIES. *W. H. Sheldon, O. W. Freeman (by invitation), J. S. Wilson (by invitation) and A. J. Merrill.* Depts. Pathology and Medicine, Emory University School of Medicine and Grady Memorial Hospital, Atlanta, Ga.

Seventeen renal needle biopsies were obtained from sixteen patients. Glomerulonephritis was encountered eight times and "lower nephron nephrosis" twice. Lupus, cortical necrosis, arteriolonephrosclerosis, pyelonephritis, multiple myeloma, tubular cytoplasmic dispersion and adenocarcinoma were each diagnosed once. Adequate follow-up has been obtained in ten instances, six times by autopsy and four times by clinical and laboratory data. The biopsy confirmed the clinical impression in ten instances. In five instances the morphologic diagnosis changed the clinical impression. In one case the histologic study was inconclusive and in another the morphologic findings were interpreted incorrectly.

Complications occurred in three instances. In two anuric patients blood clots formed in the renal pelvis. This complication was subsequently avoided by irrigation through a ureteral catheter. In another patient with glomerulonephritis and severe anemia massive bleeding occurred.

In selected patients renal needle biopsy appears to be a valuable diagnostic tool.

RELATIONSHIP OF ALCOHOLISM AND HEAT PYREXIA. *Emitt H. Shoemaker (by invitation) and Ellard M. Yow.* Dept. Internal Medicine, Baylor University College of Medicine, and the Ben Taub Infectious Disease Laboratory, Jefferson Davis Hospital, Houston, Tex.

There are four effects of heat of clinical significance: heat cramps, heat exhaustion (shock syndrome), anhidrotic heat exhaustion, and heat pyrexia. The first three account for most of the morbidity and the last for all of the mortality. The environmental factors important in the production of heat pyrexia are high temperatures and particularly high relative humidity. Early observers noted the increased incidence of heat stroke in alcoholics. This has been attributed to the pharmacologic effect of alcohol. The present study deals with observations made on twelve patients seen in 1951 during a severe heat wave and six seen during a less severe heat wave in 1953. The average age in both of these groups was considerably less than that reported in the literature. All of the patients in both groups were white and had acute alcoholism and most were chronic alcoholics. The recovery in these patients was related to the degree and duration of the hyperthermia, the state of the peripheral circulation and the promptness with which the temperature was reduced to normal. The only patients dying after the first few hours of admission died with severe liver disease.

RETINAL CIRCULATION DURING ALTERATIONS IN PERFUSION PRESSURE. *H. O. Sieker (by invitation) and J. B. Hickam.* Dept. Medicine, Duke University School of Medicine, Durham, N. C.

Previous investigations have demonstrated that the normal retinal vessels change their size when the arterial oxygen tension is altered and that this response is greatly impaired in diabetic and hypertensive retinopathy. This study was undertaken to determine the effect of

variations in perfusion pressure on the caliber of the fundal vessels in normal subjects and patients with postural hypotension. Eyeground photographs were obtained under constant photographic conditions on subjects in the erect and recumbent position while breathing air and 100 per cent oxygen, during and after the Valsalva maneuver and during neck compression. In the normal erect subject the retinal vessels were larger than when recumbent and the magnitude of change was similar to that observed with variations in arterial oxygen tension. The same response was observed in patients with postural hypotension, with a fall in blood pressure before syncope occurred. The Valsalva maneuver and neck compression produced slight alterations in vessel size. This evidence suggests that the retinal circulation is continuously adjusted to maintain a constant retinal oxygen tension. It is postulated that these mechanisms have a role in maintaining normal circulation of the brain and retina and that their impairment may be a factor in the development of some retinopathies.

OBSERVATIONS ON MALNOURISHED PATIENTS WITH EDEMA. *W. A. Sodeman and K. L. Mukherji (by invitation)*, School of Medicine, University of Missouri, Columbia, Mo., and School of Tropical Medicine, Calcutta, India.

Eight famine victims in Calcutta were selected on the basis of (1) malnutrition resulting from inadequate diet and (2) the development of edema in the course of the illness. In some, diuresis occurred at onset of treatment, accompanied by a reduction in weight and in the thiocyanate space with little change in the plasma volume. In four such patients the weight stabilized, minimal edema gradually receded, the thiocyanate space diminished, and plasma volume increased. Diuresis was constant and disproportionately great for the change in thiocyanate space. In two patients diuresis continued during a period of relatively constant weight, and plasma volume and thiocyanate space did not change appreciably. In two, recurring clinical edema followed a primary diuresis during which the clinical edema present on admission had cleared entirely. There was no appreciable change in body weight, the effect presumably resulting from internal shifts in body water.

These data indicate that in the edema studied, important water shifts occurred other than those between vascular and extracellular space, presumably between tissue cells and the extracellular space, suggesting the importance of the participation of the tissue cells in the edematous state studied and in the fundamental mechanism of the edema.

BIOASSAY OF ORAL DIURETICS. *Charles L. Spurr, Ralph V. Ford (by invitation) and John H. Moyer.* V. A. Hospital and the Depts. Medicine, and Pharmacology, Baylor University College of Medicine, Houston, Tex.

Four drugs were selected for study: neohydrin,® 60 mg.; diamox,® 750 mg.; dirnate,® 6 gm.; cumertilin,® 60 mg. The drugs were given in three divided doses daily for two consecutive days. Patients with minimal heart failure controlled on constant sodium intake, which resulted in slow retention of fluid, were followed by measurement of electrolyte excretion (Na, K, Cl), urine volume and body weight. Diuretics were given only at a constant baseline weight for each patient.

In support of the use of sodium excretion as a measure of response to a diuretic, the following two facts were noted: First, on the basis of a large number of tests of both oral and parenteral diuretics, a reasonable correlation between sodium excretion increase and additional water loss was found. Second, the response to the diuretics was more consistent when measured in terms of sodium excretion than in terms of water excretion. Indeed, the coefficient of variation ($s/\bar{x}$) was larger for water loss than for sodium excretion in twelve of thirteen series of tests. A simple, non-parametric test shows that this result is statistically significant ($P = 0.0026$), and hence the coefficient of variation cannot be regarded as equal for the two measures. The coefficient of variation for body weight change was three to five times larger than that for water excretion.

The mean increase in mEq. of sodium excretion was as follows: neohydrin, 51.27 ± 25.48; diamox, 50.9 ± 28.85; dirnate, 37.3 ± 28.72; and cumertilin, 20.79 ± 18.68. The standard error was 31—constant in each case. While these levels of sodium excretion are not statistically distinct, there is a difference in distribution of the response to the four drugs into two groups. The first group with a mean sodium increase to 16, which was smaller than the standard error of the control sodium excretion, consisted of 78 per cent of the patients receiving cumertilin,

57 per cent dirnate patients, 33 per cent neohydrin, and 14 per cent diamox. The second group with a mean sodium increase of 45 to 91 mEq. consisted of 76 per cent of the patients receiving diamox, 67 per cent of those receiving neohydrin, 43 per cent dirnate and 22 per cent cumertilin.

SURVIVAL OF HUMAN ERYTHROCYTES TAGGED WITH RADIOACTIVE CHROMIUM: A METHOD YIELDING RESULTS COMPARABLE TO THE ASHBY TECHNIC. *D. A. Sutherland (by invitation), Mary Sue McCall (by invitation), Margaret T. Groves (by invitation) and E. E. Muirhead.* Radioisotope Unit, Dallas V. A. Hospital and Depts. Medicine and Pathology of the Southwestern Medical School of the University of Texas, Dallas, Tex.

The following method for the estimation of the survival of erythrocytes by radioactive chromium yields results comparable to the Ashby technic. The plasma from 50 to 65 ml. of blood is withdrawn, set aside and the RBC are incubated with saline having 200 to 300 microcuries of Cr^{51} (Na_2 Cr^{51} O_4) for one hour at 37°C. while agitated. The RBC are washed three times with cold saline, resuspended in the original plasma and given intravenously. The twenty-four-hour sample is the initial 100 per cent reference. Radioactivity of samples (4 ml. daily for three to five days, then weekly) and correction for decay are measured in a sodium iodide-thallium scintillating well-type crystal. The ratio of radioactivity of each sample to the activity at twenty-four hours is plotted against time in days on linear coordinate paper.

Five normal humans received 1 pint of blood for the Ashby technic a segment of which was tagged with Cr^{51}. The results of the two methods are in the table following:

Case	Per cent Loss per Day	
	Ashby	Cr^{51}
1	0.88	1.0
2	0.82	0.85
3	0.91	0.85
4	0.98	0.94
5	0.95	0.91
Average	0.91	0.91

In five additional normals the survival of their own RBC tagged with Cr^{51} gave results as in the table. With Cr^{51} tagging the curve of degradation in normals has been smooth, slightly curvilinear, with extinction at 100 to 112 days.

HOMOZYGOUS HEMOGLOBIN C: A NEW HEREDITARY HEMOLYTIC DISEASE. *Douglas W. Terry, Arno Motulsky and Charles E. Rath (introduced by Harold Jeghers).* Dept. Medicine, Georgetown University Hospital and Walter Reed Army Medical Center, Washington, D. C.

A forty-four year old Negress had arthralgia, splenomegaly and mild microcytic anemia. Paper electrophoresis revealed 100 per cent type C hemoglobin. Less than 1 per cent fetal hemoglobin was detected by alkaline denaturation. Sickling was negative. Blood films revealed many target cells, fragmented cells and rare normoblasts. Reticulocytes were 2.1 per cent. The bone marrow showed moderate normoblastic hyperplasia. Osmotic fragility was decreased and mechanical fragility slightly increased. Fecal urobilinogen was increased. Transfused normal cells had a survival of 106 days demonstrated by serial quantitative electrophoretic determinations. This excluded an extracorpuscular hemolytic mechanism. Cr^{51} and Ashby studies of the patients' red cells were consistent with a survival of approximately sixty days.

Family study showed four siblings and two living daughters to be heterozygous carriers of Hb C (34–40 per cent Hb C). Both daughters and a niece with Hb C trait had frequent episodes of arthralgia. Target cells were prominent and osmotic fragility was decreased in C trait patients without further evidence of hematologic disease.

The clinical and hematologic picture of homozygous Hb C as found in several other yet unpublished cases has closely resembled the findings in our patient and must be differentiated from Thalassemia minor. Homozygous Hb C disease, a genetic counterpart of sickle cell anemia, represents a definite new hematologic entity.

HUMAN SERUM ALBUMIN TAGGED WITH I^{131} IN PATIENTS WITH ASCITES CAUSED BY ABDOMINAL CARCINOMATOSIS OR HEPATIC CIRRHOSIS: THE RATES OF INTERCHANGE BETWEEN THE VASCULAR COMPARTMENT OF PERITONEAL CAVITY. *Malcolm P. Tyor (introduced by Arthur C. Guyton).* Medical Division, Oak Ridge Institute of Nuclear Studies, Oak Ridge, Tenn.

Tracer amounts of iodinated albumin were injected either intraperitoneally or intravenously into eleven patients with ascites; nine had abdominal carcinomatosis and two had cirrhosis. With either route of administration the rates of decreasing concentration of radioactivity in the injected compartment and increasing concentration in the other were similar after the initial twelve to twenty-four hours. The level of specific activity of albumin in the injected compartment and in the other approached an equilibrium in all patients studied. The rate of interchange of albumin between the two compartments was represented by the slope of the linear plot obtained from the differences between the specific activities of the plasma and ascitic fluid. The half-times were found to be fourteen to fifty-one hours for intraperitoneal injection and twenty-one to fifty-five hours for intravenous injection.

The data indicate that the plasma and ascitic fluid albumin are in constant exchange, in conformance with the concept of the dynamic equilibrium of body proteins.

RENAL TUBULAR PHENOMENA UNDER THE INFLUENCE OF A CARBONIC ANHYDRASE INHIBITOR. *L. G. Welt, D. T. Young (by invitation) O. A. Thorup, Jr. (by invitation) and C. H. Burnett.* Dept. Medicine, School of Medicine, University of North Carolina, Chapel Hill, N. C.

A carbonic anhydrase inhibitor was administered to three normal male subjects when they were in a state of physiologic diabetes insipidus and who had been made mildly acidotic by the ingestion of 15 gm. NH_4Cl/day for five days. The inhibitor promoted: (1) striking increase in the rates of excretion of water, sodium, bicarbonate and total solutes; (2) lesser increases of potassium and chloride; (3) diminution in ammonia and titratable acid and (4) an increase in urine pH.

An increased rate of excretion of water superimposed on a state of physiologic diabetes insipidus implies the delivery of a larger volume of fluid from the proximal to the distal tubule. This is due to a decrease in active proximal reabsorption of solutes which in this instance were predominantly sodium and bicarbonate. This, in turn, implies that secretion of H^+ normally occurs in the proximal as well as the distal tubule.

The increase in urine flow was composed of free as well as osmolar water. Hence, there must have been an increase in distal solute reabsorption in consequence of the increased volume of isosmotic fluid reaching the distal tubule. This contradicts the concept of a fixed distal tubular maximum for solute reabsorption.

VIREMIA IN ACQUIRED HEMOLYTIC ANEMIA AND RELATED RETICULO-ENDOTHELIAL DISEASES. *J. B. Workman (by invitation), A. B. Snider (by invitation) and Theodore E. Woodward.* Section of Infectious Diseases, Dept. Medicine, University of Maryland School of Medicine, Baltimore, Md.

Seventy blood specimens obtained from thirty-one patients with acquired hemolytic anemia were tested for the presence of hemagglutinating viruses. Auto-agglutination of erythrocytes was present in all patients and a positive antiglobulin test was found in the twenty-eight so tested. In addition, blood was examined from thirty patients with diagnoses including; lymphomas, collagen disorders and infectious mononucleosis. None of this group displayed hemolytic activity and only a small number of those tested demonstrated erythrocyte bound antibody.

Virus isolation was attempted in all subjects, utilizing standard embryonated egg technics. Neutralization and hemagglutination-inhibition tests for Newcastle disease virus were performed and allanto-amniotic fluid harvested from the inoculated eggs was tested for the presence of hemagglutinating viruses with human erythrocytes.

Ten blood samples from four of the cases of acquired hemolytic anemia were studied by electron microscopy. The presence of "virus-like" particles was detected on the surface of some of the erythrocytes of one of these patients.

Approximately 15 per cent of the 130 blood specimens examined gave evidence suggestive of Newcastle disease virus infection. However, in no instance was definite virus identification established. Studies for the presence of viruses other than that of Newcastle disease are in progress. In a few instances, notably lupus erythematosus and certain lymphomas, there is evidence of an unidentified, non-bacterial agent which is transmissable in eggs. At present, the "virus-like" bodies described in these conditions have not been established as etiologic agents rather than mere coincidental findings.

ACHROMYCIN®—A NEW FORM OF AUREOMYCIN. *William B. Young and James G. Tuttle (introduced by George T. Harrell, Jr.).* Dept. Internal Medi-

cine, Bowman Gray School of Medicine, Winston-Salem, N. C.

Gastrointestinal side effects from the administration of aureomycin often require its discontinuance. Achromycin® hydrochloride (tetracycline hydrochloride) is a modification of aureomycin with the chlorine removed, but it appears to have the same broad antibacterial and antirickettsial spectrum. It is said to be well tolerated after oral or intravenous administration and adequate blood and spinal fluid levels are attained.

Achromycin was given to thirty-one patients with various infections: urinary, thirteen, respiratory, sixteen, endometritis, one, cholangitis, one, appendiceal abscess, one. A daily dose of 1 to 3 gm. was given for two to fifteen days. Thirteen gram-negative and gram-positive organisms singly or in combination were recovered from the patients.

Bacteriologic and clinical responses were considered good (eight cases), satisfactory, thirteen, fair, four and unsatisfactory, four. Two cases are still under bacteriologic study. In our experience achromycin was therapeutically equal to aureomycin. No toxic effects or hemolytic changes were noted. Three instances of gastrointestinal side effects (9.7 per cent) were noted but the drug did not have to be discontinued in any case. The symptoms reported were: transient nausea on the fourth day of treatment, one; slight looseness but no increase in number of stools, one; nausea, vomiting and diarrhea on the third and fourth day of treatment subsiding without discontinuance of the drug, one. Eight reported a peculiar taste during treatment but only one complained of it; three described it as metallic, two as bitter, one as "salty," one as "bad" and one as "peculiar." Achromycin appears to produce fewer gastrointestinal side effects than aureomycin.

RENAL CLEARANCE MEASUREMENTS OF INULIN AND p-AMINOHIPPURATE IN PATIENTS WITH MYXEDEMA. *Ernest Yount (by invitation) and J. Maxwell Little.* Depts. Medicine, Physiology, and Pharmacology, Bowman Gray School of Medicine, Wake Forest College, Winston-Salem, N. C.

Renal clearances of inulin and p-aminohippurate (PAH) have been measured in two male and five female patients with myxedema. The results for C_{IN}, C_{PAH}, renal blood flow, in ml., and filtration fraction (FF), corrected to 1.73 m^2, were respectively: (males) 86.5, 250, 641, 0.346; 49.4, 244, 387, 0.206; (females) 57.7, 340, 516, 0.186; 92.7, 330,502, 0.280; 75.5, 315, 523, 0.248; 40.0, 153, 228, 0.260; 42.2, 299, —, 0.142. Comparing these results with normal measurements ($\bar{X}$) and standard deviations (σ) obtained by Homer W. Smith, our patient distribution is as follows: C_{IN}, $< \bar{X} - 2\sigma = 5$, $< \bar{X} - 1\sigma = 2$; C_{PAH}, $< \bar{X} - 2\sigma = 3$, $< \bar{X} - 1\sigma = 4$; FF, $< \bar{X} - 1\sigma = 1$, $\bar{X} \pm 1\sigma = 2$, $> \bar{X} + 1\sigma = 2$, $> \bar{X} + 2\sigma = 2$. The above indicates that the tendency in myxedema is for the glomerular filtration rate, renal plasma flow and renal blood flow to be decreased. The values for filtration fraction are more variable and no clear pattern is evident.

COMBINED STREPTOMYCIN AND ERYTHROMYCIN THERAPY IN SUBACUTE BACTERIAL ENDOCARDITIS. *Ellard M. Yow, Lloyd C. Jones (by invitation) and Ray E. Flake (by invitation).* Dept. Internal Medicine, Baylor University College of Medicine and the Ben Taub Infectious Disease Laboratory, Jefferson Davis Hospital, Houston, Tex.

While there have been striking advances in the therapy of endocarditis since the discovery of penicillin, there are still therapeutic failures in about 20 per cent of cases. The present study was undertaken in an attempt to evaluate the effect of erythromycin, alone and in combination with other antibiotics, in the treatment of patients with endocarditis failing to respond to previous therapy. Ten patients were treated, including one with an acute micrococcic endocarditis, another with subacute micrococcic endocarditis and eight with streptococcal endocarditis.

Erythromycin was administered alone to three patients, resulting in a transient suppression of the infection in one. It was given in combination with streptomycin to eight patients. There was bacteriologic and clinical evidence of cure in six of these patients. One died of heart failure during therapy and in another the organism was found to be resistant to streptomycin. This patient responded to treatment with erythromycin and bacitracin.

It may be concluded from this study that erythromycin alone is of little value in the treatment of endocarditis. When used in combination with streptomycin against susceptible organisms it was effective in six patients.

Case Report

Dystrophia Myotonica with Associated Sprue-like Symptoms*

K. K. KAUFMAN, M.D. *and* E. W. HECKERT, M.D.
Wood, Wisconsin

DYSTROPHIA myotonica (myotonia atrophica) is a familial disorder characterized by presenile cataracts, endocrine disturbances and slowly progressive muscle atrophy associated with delay in relaxation of affected muscles, usually first noticeable in the face, neck and forearm.

The etiology of the disease is unknown. However, it usually occurs in males with the age of onset most often between fifteen and forty years or later when appearing for the first time in a family.

Pathologic changes may be found in the musculature whether skeletal, cardiac or smooth and in the endocrine glands. Microscopic alterations involving the muscle tissue consist of destruction, swelling, loss of striations, hyalinization, replacement by fat and increase in sarcolemma nuclei. Normal and degenerated muscle fibers may be found together in the same microscopic field. Bevans in 1945 described nonspecific pathologic findings in the gastrointestinal tract similar to skeletal muscle changes but much less severe than those found in scleroderma.

The case to be described is unusual not only by virtue of its rarity as a myopathy but also because of the presence of persistent steatorrhea which, in association with nausea, vomiting and diarrhea, made up the bulk of the patient's original complaints. In Bevan's group of four cases steatorrhea was not included in the gastrointestinal symptomatology.

CASE REPORT

A fifty-two year old white male was admitted to the Hospital with a chief complaint of inability to hold up his head without support, of three months' duration. In 1948 following a left inguinal herniorrhaphy, the patient noted the onset of easy fatigability. In the autumn of 1949 he began having almost weekly episodes of vomiting and diarrhea with light-colored watery stools. Intolerance of fatty foods also developed. In January, 1949, his weight began to decrease, amounting to a 50 pound loss by May, 1950. Later in that month he was admitted to another hospital where significant findings included flat oral and normal intravenous glucose tolerance tests, serum carotene level of 0.1 mg. per cent, 69 international units of vitamin A and gastrointestinal x-rays revealing abnormality in the upper jejunum and distal duodenum consistent with scleroderma. Following that hospitalization he remained asymptomatic until the onset of steatorrhea in November, 1950. One month later the patient began noting weakness of the arms. Neck muscle weakness, with difficulty in holding the head erect for periods longer than several hours, appeared in January, 1951. This weakness became progressively more severe and since April of that year he has been unable to hold up his head without support. There was loss of libido since February, 1950.

Physical examination revealed a poorly developed and poorly nourished white male with a temperature of 98°F., pulse rate of 52, and blood pressure of 110/65. The voice was monotonous with a nasal tone. Atrophy of the temporal muscles was noted along with frontal alopecia. Axillary hair was absent and pubic hair was sparse. Peripheral lenticular opacities of the senile type were present bilaterally. Patellar reflexes were diminished and ankle jerks were absent bilaterally. Muscle atrophy was generalized and symmetrical but most marked in the

* From the Veterans Administration Hospital, Wood, Wis., and Marquette University School of Medicine, Milwaukee, Wis. Published with permission of the Chief Medical Director, Department of Medicine and Surgery, Veterans Administration, who assumes no responsibility for the opinions expressed or conclusions drawn by the authors.

sternocleidomastoids, trapezii, rhomboids, neck extensors, erectores spinae, abdominalis sartorii and abductors of the thigh. Mechanical myotonia was most pronounced in the hands and arms. Due to the atrophy, the patient had a "hatchet" face and a "pole neck." He walked with his trunk bent forward as if he had rheumatoid disease of the spine. However, it became apparent that this was not so when he would attempt to straighten up. He would use the muscles of his arms to crawl up a chair to straighten up and push on his chin to make his head erect.

Laboratory examinations included 4,100,100 red blood cells, 12.5 gm. hemoglobin, and a hematocrit of 40. The serum amylase level was 27 mg. per cent. The oral glucose tolerance test was flat. Gastric analysis showed hypoacidity. Twenty-four hour urinary creatine excretion was 177 mg. Total serum proteins were 5 gm., with 3.6 gm. albumin and 1.4 gm. globulin per 100 ml. Fat globules were present in the stools.

Vitamin A absorption curves were flat according to the method of study wherein 200,000 units of vitamin A was administered orally, followed by determination of serum levels of vitamin A at time of administration as well as at intervals of three, five and eight hours thereafter. Fasting vitamin A ester of the serum was 149 units/100 ml., and 155, 138 and 166 units/100 ml. at intervals of three, five and eight hours, respectively. Fasting vitamin A alcohol of the serum was 151 units/100 ml. and 142, 149 and 155 units/100 ml. at the designated time intervals thereafter. Fecal fat determinations on two occasions were 47.7 per cent and 60 per cent.

Twenty-four hour 17-ketosteroid determination showed 4.4 mg. before administration of ACTH and 6.4 mg. following administration of 95 mg. ACTH intramuscularly over a forty-eight-hour period. Normal findings included urinalysis, serologic tests, white blood count and differential, erythrocyte sedimentation rate, serum non-protein nitrogen, phosphorus and calcium, prothrombin time, fasting blood sugar, spinal fluid, stool cultures for acid-fast bacilli, four-hour Thorn test, x-rays of the chest, skull, spine, colon and proctoscopy.

The gallbladder was not visualized on x-ray study. Gastrointestinal series revealed moderately redundant second portion of the duodenum and dilatation of the loops of the small bowel with markedly delayed gastrointestinal motility. Electrocardiograms showed sinus bradycardia and myocardial damage on the basis of low voltage. Smear of the sternal bone marrow was normal; examination of the clotted specimen was interpreted as showing normoblastic hyperplasia. Skin and muscle biopsy from the right deltoid area revealed the epithelium to be atrophic with considerably increased pigmentation of the malpighian layer. Many of the cells in that area showed pyknosis of their nuclei. There was also considerable increase in the collagenous tissue of the corium. Atrophy of the skin appendages and slight thickening of the arteriolar walls were present. The muscles were atrophic in regard to size but showed no degenerative changes. The biopsy diagnosis made was pigmented atrophy of the skin.

Bilateral testicular biopsy revealed focal areas of complete atrophy of the seminiferous tubules. The other tubules showed slight thickening of the basement membrane. Mature sperm were seen. The diagnosis was focal atrophy.

COMMENTS

The first symptoms of a patient afflicted with this disease are usually weakness and fatigue. Soon thereafter the muscles of the face, tongue, neck, forearms and later of the lower extremities become atrophic. The wasting of the neck muscles and face muscles give the patient a "hatchet face" and "pole neck." The speech is usually monotonous and has a nasal twang. Marked atrophy of the sternocleidomastoid and trapezii muscles results in inability to hold the head erect. Involvement of the cardiomusculature causes bradycardia. The mechanical irritation of the affected muscles is increased. There is usually myotonic reaction which is elicited by tapping the muscles. The atrophic muscles contract rapidly and relax very slowly. There may be fibrillation present. Bevans, in his report of four cases, described gastrointestinal disturbances and changes in the musculature similar to the changes in skeletal muscles.

This disorder must be differentiated from myotonia congenita. The presence of "hatchet face," presenile cataracts and endocrine disturbances usually aids to make the diagnosis. The latter disease is a congenital disorder and comes on in early childhood.

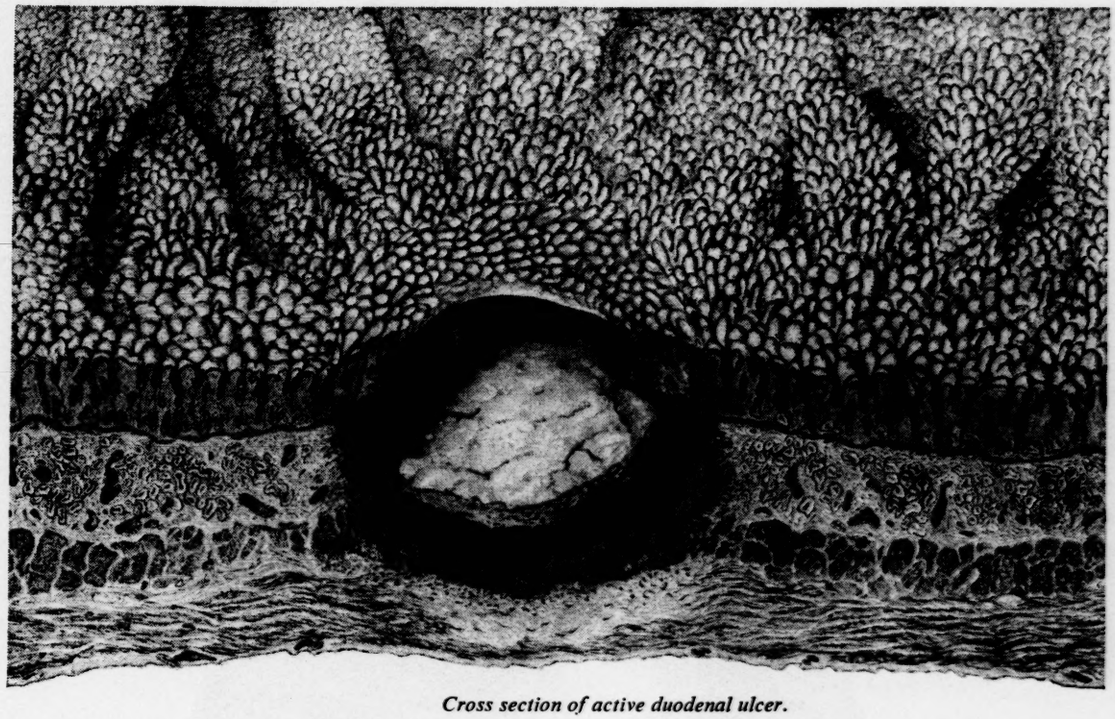
From a laboratory standpoint the steatorrhea fits into a sprue-like syndrome with impaired intestinal absorption as indicated by increased fecal fat, flat oral glucose tolerance curve and

low vitamin A ester and vitamin A alcohol tolerance curves. The sprue-like symptomatology in this case is attributed to atrophy of the small intestinal musculature.

The neurologic type of muscular atrophy, myotonia, lenticular opacities, testicular atrophy, frontal alopecia, electrocardiographic abnormalities, low 17-ketosteroid excretion and normal adrenal cortex response to ACTH all point to the diagnosis of dystrophia myotonica.

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Cross section of active duodenal ulcer.

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Panthoderm Cream is soothing, bland, non-irritating... clean, snow-white, non-staining; water-miscible, spreads readily; easily removed without injury to granulating tissues.



2 oz. and 1 lb. jars; 1 oz. tubes.

quickly relieves pain, itching and inflammation

soothes, softens, lubricates

promotes granulation and speeds healing

non-toxic and virtually non-sensitizing

1. Kline, P. R., and Caldwell, A.: New York St. J. M. May 1, 1952.
2. Combes, F. C., and Zuckerman, R.: J. Invest. Dermat. 16:379, 1951.
3. Kline, P. R.: Current News in Derm. & Syph., May 1952.

samples and literature upon request

u.s. vitamin corporation
Casimir Funk Laboratories, Inc., (affiliate)
250 East 43rd Street, New York 17, N.Y.

compare before you prescribe

modern criteria of good digitalis therapy

1. pure active principle
2. complete absorption
3. rapid onset of action
4. smooth, even maintenance
5. frequent dosage readjustment unnecessary
6. virtual freedom from gastric upset

digitaline nativelle®

conforms to the rigid criteria of a modern cardiotonic and provides oral, I.M., and I.V. forms for flexibility of dosage

compare *then prescribe...*

DIGITALINE NATIVELLE

—the original pure crystalline digitoxin

Consult your Physicians' Desk Reference for dosage information.

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GANTRISIN
'Roche'

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a single, soluble, wide-spectrum sulfonamide

When in doubt about antibacterials—

With so many antibacterial drugs to choose from, you may wonder which one to prescribe. We believe you'll agree that most of them are rather good. Still, we hope you'll try Gantrisin 'Roche'...because this single sulfonamide is soluble in both acid and alkaline urine...because it has a wide antibacterial spectrum...an impressive clinical background...and, above all, because it's so well tolerated by most patients.

Gantrisin®-- brand of sulfisoxazole

NEW...council-accepted oral anticoagulant

(not a coumarin derivative)

with a wide range of safety

HEDULIN®

(Brand of Phenindione, 2-phenyl 1,3-indandione)

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Permits dependable prothrombin control with little risk of dangerous fluctuations

- **HEDULIN is not cumulative in effect—provides greater uniformity of action and ease of maintenance**
- **HEDULIN is rapidly excreted—therapeutic effect dissipated within 24-48 hours if withdrawal becomes necessary**
- **HEDULIN acts promptly, producing therapeutic prothrombin levels in 18-24 hours**
- **HEDULIN requires fewer prothrombin determinations—only one in 7 to 14 days, after maintenance dose is established**
- **HEDULIN's anticoagulant action is rapidly reversed by vitamin K_1 emulsion**



DOSAGE: 4 to 6 tablets (200 to 300 mg.) initially, half in the morning and half at night; maintenance dosage (on basis of prothrombin determinations daily for first three days), 50 to 100 mg. daily, divided as above.

Available on prescription through all pharmacies, in original bottles of 100 and 1000 50-mg. scored tablets.

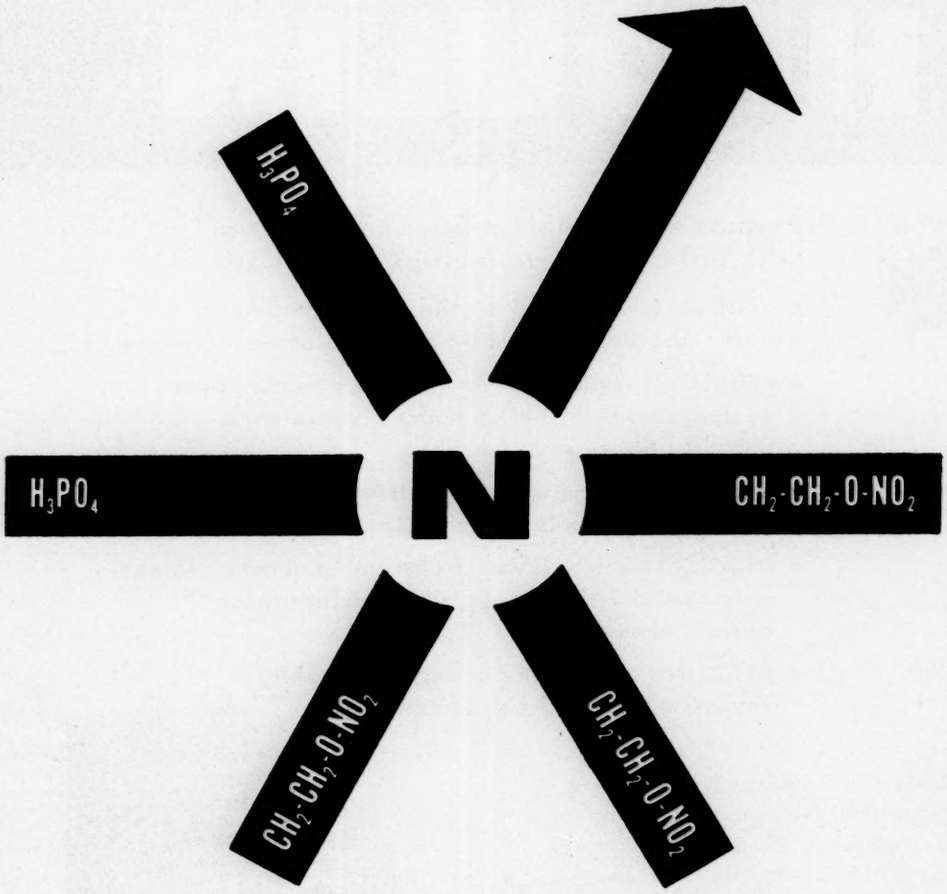
Complete literature to physicians on request

Walker® **LABORATORIES, INC., MOUNT VERNON, N. Y.**

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See the chemical difference

in this unique, amino nitrate



METAMINE® is chemically unique, because its three nitrate groups are nitrogen (amino)-linked, rather than carbon-linked. And METAMINE has the smallest effective dose (2 mg.) of any long-acting cardiac nitrate for prevention of angina pectoris—with correspondingly few side effects.

Thos. Leeming & Co. Inc. 155 EAST 44TH STREET, NEW YORK 17, N.Y.

...and the clinical difference!

for prevention of angina pectoris

Fewer attacks of angina pectoris, less severe attacks, or no further attacks are the benefits your patients may expect of routine preventive therapy with METAMINE tablets.[1] Milligram for milligram, METAMINE appears most efficient of all the new, long-acting coronary vasodilators.[2] Even during prolonged treatment, side effects are mild and infrequent. Resistance and methemoglobinemia have not been reported, nor is blood pressure altered.

The beneficial actions of METAMINE appear to affect the entire circulation,[3] reducing the cardiac work-load and oxygen requirement to permit a life of useful activity for the anginal patient.

Dosage to prevent angina pectoris: 1 tablet (2 mg.) after each meal, and 1 to 2 tablets (2 to 4 mg.) at bedtime. Full preventive effect is usually attained after the third day.

METAMINE is supplied in bottles of 50 and 500 tablets.

Metamine®

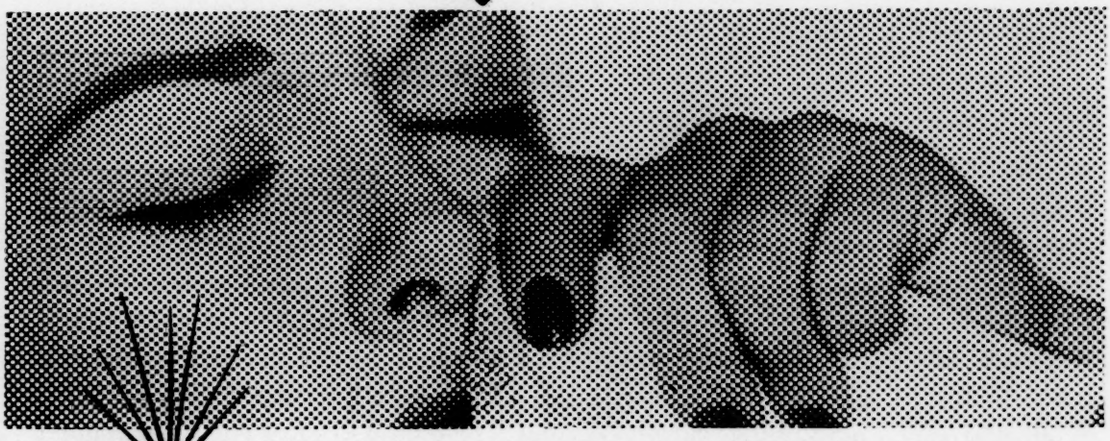
Triethanolamine trinitrate biphosphate, Leeming, tablets 2 mg.



REFERENCES:

1. *Palmer, J.H., and Ramsey, C.G.: Canadian M.A.J., 65:16, July, 1951; P. Dailheu-Geoffroy: La Clinique, 46:27, May 1951.*
2. *Melville, K.I., and Lu, F.C.: Canadian M.A.J., 65:11, 1951.*
3. *Pfeiffer, H.: Klin. Wochenschr., 28:304, 1950.*

allergy or infection?





Whether the rhinitis or sinusitis is allergic or bacterial in nature, Biomydrin Nasal Spray is indicated because it is an effective antiallergic, antibacterial and decongestant. Moreover, Biomydrin contains *Thonzonium Bromide,* an exclusive ingredient synthesized in our laboratories, which is an extremely potent antibacterial and synergistically enhances the action of the antibiotics in Biomydrin; in addition, Thonzonium Bromide is an effective mucolytic and reduces surface tension, making it possible for Biomydrin to penetrate mucoid secretions, spread over the nasal tissues, and remain in contact with the mucosa for prolonged action.

Adults: 2 or 3 sprays in each nostril, 4 or 5 times a day as needed, or as directed by physician.

Children: 1 or 2 sprays in each nostril, 4 or 5 times a day as needed, or as directed by physician.

Supply: ½ ounce plastic atomizer. Available on prescription only.

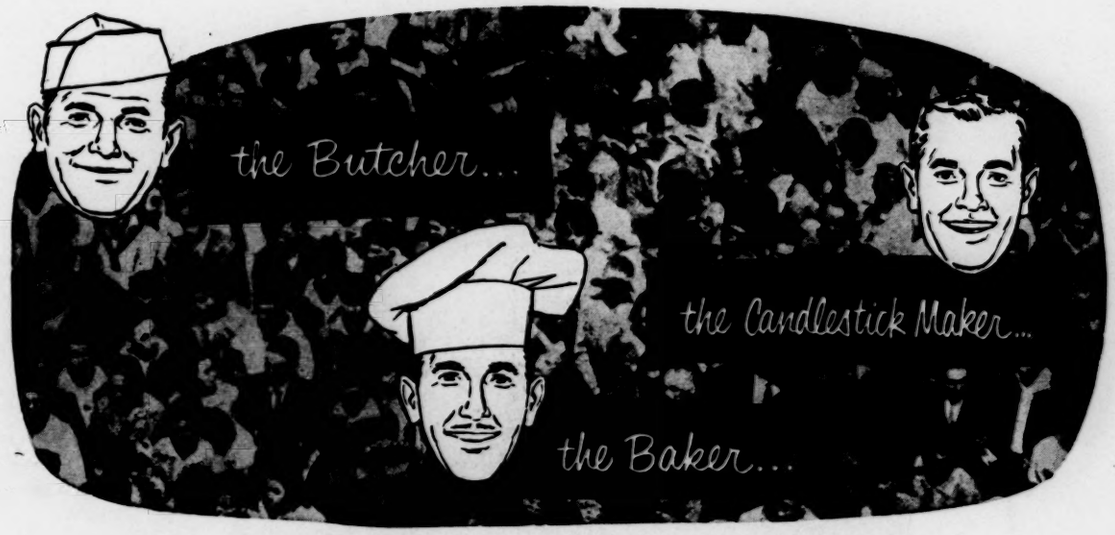
in infectious and allergic rhinitis and sinusitis

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NASAL SPRAY

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What does Enriched Bread give him Nutritionally?

CONSERVATIVE industry estimates indicate that the per capita consumption of bread in the United States is 5 ounces daily. Since the bulk of this output is enriched white bread, the amounts of essential nutrients supplied by this quantity become significant from a standpoint of national health.

Contrary to widespread belief, enriched bread is considerably more than merely a source of caloric food energy. As the table indicates, 5 ounces of enriched bread supplies for a sedentary man, the following substantial proportions of his daily needs for these important nutrients: protein, 17%; thiamine, 28%; riboflavin, 12%; niacin, 26%; iron, 31%; calcium, 13%. Five ounces of bread also provides 16% of the daily caloric need.

This generous nutrient contribution is made at a cost of but a few cents, a fact which has led bread to be called a bargain in food.

Some twelve years ago, enriched bread came into widespread commercial production as a result of cooperation between industry and health authorities in the aim to improve the nutritional status of the American people. It has made a significant contribution to the improvement of national health and to the reduced incidence of severe and mild nutritional deficiency states.

The Seal of Acceptance denotes that the nutritional statements made in this advertisement are acceptable to the Council on Foods and Nutrition of the American Medical Association.



NUTRIENTS AND CALORIES CONTRIBUTED BY 5 OUNCES OF ENRICHED BREAD AND THEIR PERCENTAGES OF RECOMMENDED DAILY DIETARY ALLOWANCES*

Nutrients and Calories	Protein	Thiamine	Riboflavin	Niacin	Iron	Calcium†	Calories
Amounts	12. Gm.	0.34 mg.	0.21 mg.	3.1 mg.	3.7 mg.	125 mg.	391
Percentages of Allowances	17%	28%	12%	26%	31%	13%	16%

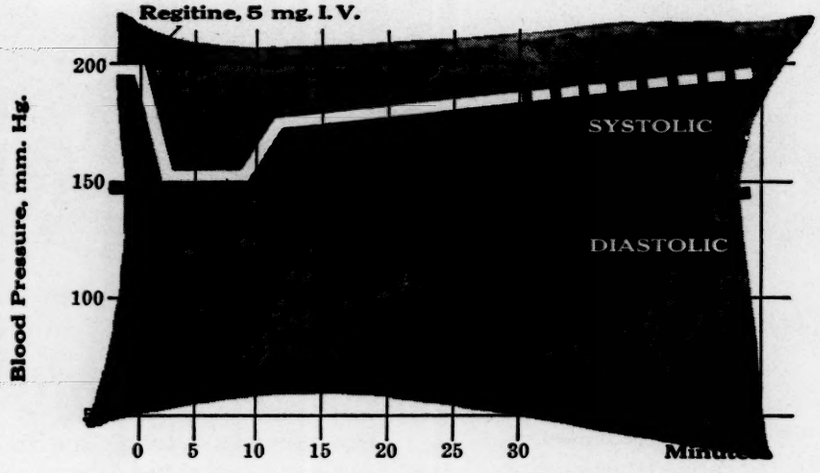
*Daily dietary allowances recommended by National Research Council for a sedentary man (154 lbs.)
†Estimated average

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PHEOCHROMOCYTOMA

causes

one curable form of hypertension



Regitine®

the preferred diagnostic agent

Because of its specificity, this potent adrenergic blocking agent affords an eminently safe, accurate, and simple test for the diagnosis of the hypertension-producing tumor – pheochromocytoma.

When it is left untreated, pheochromocytoma is a progressive and eventually fatal condition. After diagnosis, surgical removal of the tumor effects a complete cure. Therefore, "careful consideration of the possible presence of a pheochromocytoma in every patient with hypertension must now be regarded as a diagnostic obligation."[1] Testing is quickly and simply done with Regitine.

The above chart is a schematic representation of the type of response that you can anticipate in the adult hypertensive patient who does have a pheochromocytoma.

For complete information contact your Ciba Professional Service Representative or write to the Medical Service Division.

REGITINE methanesulfonate (phentolamine methanesulfonate Ciba)
REGITINE hydrochloride (phentolamine hydrochloride Ciba)

1. DECOURCY, J. L.: AM. J. SURG.–*86*:37, July, 1953.

Ciba Pharmaceutical Products, Inc., Summit, New Jersey



A new form of a synthetic narcotic analgesic . . . approximately twice as potent as racemic Dromoran (dl) Hydrobromide 'Roche' . . . inducing prompt pain relief with longer duration of analgesic effect than morphine.

. . . indicated for the relief of severe or intractable pain . . . preoperative medication and postoperative analgesia.

. . . "A striking characteristic is its ability to produce cheerfulness in pain-depressed patients the morning after an evening dose."*

. . . less likely than morphine to produce constipation, nausea or other undesirable side effects . . . whether administered orally or subcutaneously.

LEVO-DROMORAN

TARTRATE *'Roche'*

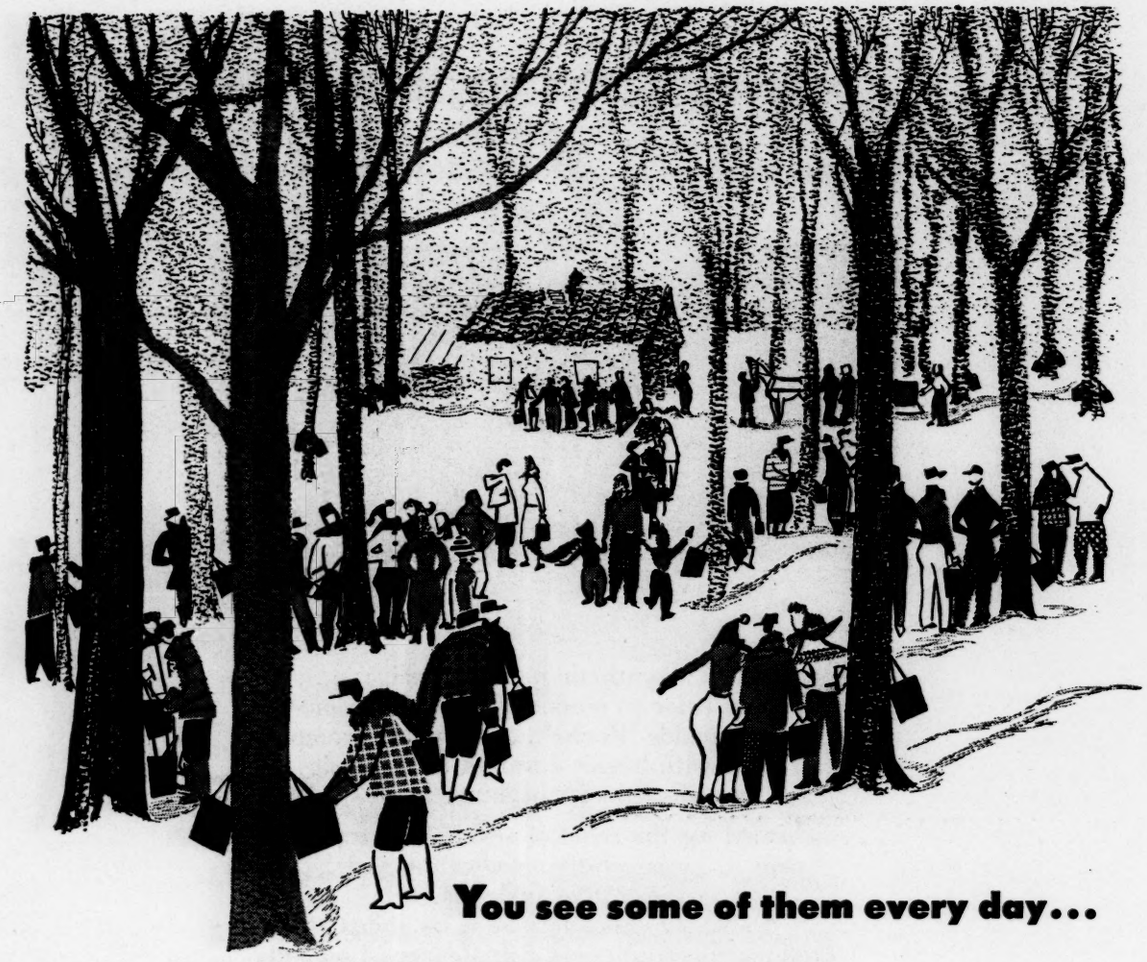
(tartaric acid salt of levo-3-hydroxy-N-methylmorphinan)

CAUTION:
Levo-Dromoran Tartrate is a narcotic analgesic. It has an addiction liability equal to morphine and therefore the same precautions should be taken in dispensing this drug as with morphine.

*Glazebrook, A. J.: Brit. M. J., 2:1328 (Dec. 20) 1952.

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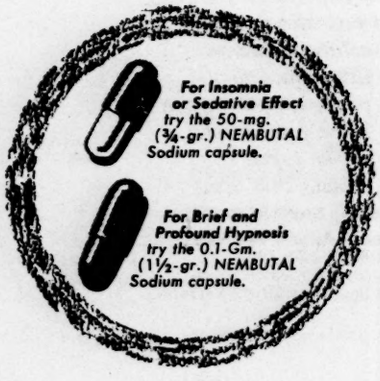
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You see some of them every day...

all the patients who represent

the 44 uses for short-acting NEMBUTAL®



● As a sedative or hypnotic *in more than 44 clinical conditions*, short-acting NEMBUTAL has established a 24-year-old record for acceptance and effectiveness. Here's why:

1. *Short-acting* NEMBUTAL (*Pentobarbital, Abbott*) *can produce any desired degree of cerebral depression—from mild sedation to deep hypnosis.*
2. *The dosage required is small—only about one-half that of many other barbiturates.*
3. *There's less drug to be inactivated, shorter duration of effect, wide margin of safety and little tendency toward morning-after hangover.*
4. *In equal oral doses, no other barbiturate combines quicker, briefer, more profound effect.*

Any wonder, then, that the use of short-acting NEMBUTAL continues to grow each year. How many of short-acting NEMBUTAL's 44 uses have *you* tried? Abbott

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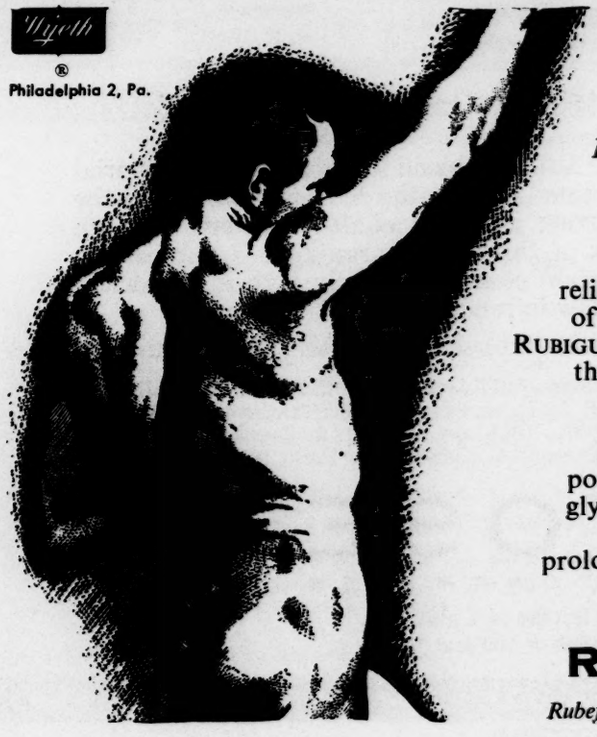
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In simple myalgia or arthropathy

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Supplied: Tubes of 1 oz.

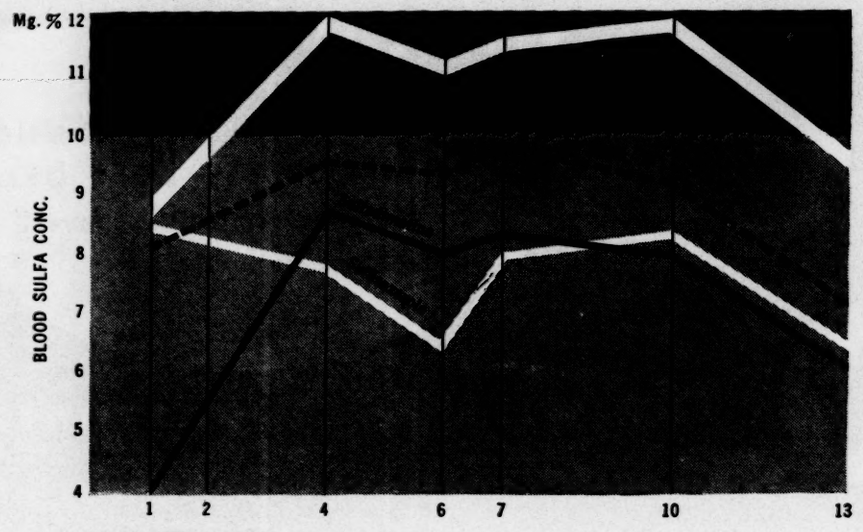
RUBIGUENT®

RUBEFACIENT CREAM, WYETH

Rubefacient • counterirritant • local analgesic

IN URINARY-TRACT INFECTIONS

FOR SUPERIOR BLOOD LEVELS[1]



1. Berkowitz, D.: Antibiotics & Chemotherapy 3:618 (June) 1953.

High where height counts,[2] SULFOSE blood levels foster antibacterial action where therapy counts—*within* the infected tissue of the urinary system.[3] For SULFOSE promotes clinical response through the potent additive attack of three sulfapyrimidines (sulfadiazine, sulfamerazine, sulfamethazine) characteristically high in blood and tissue concentrations . . . low in renal risk.[4]

Indicated in all infections due to sulfonamide-sensitive organisms.

1. Berkowitz, D.: Antibiot. & Chem. *3*:618 (June) 1953. 2. Jawetz, E.: California Med. *79*:99 (Aug.) 1953. 3. Cecil, R. L., and Loeb, R. F.: Textbook of Medicine, W. B. Saunders Co., Philadelphia, 1951, pp. 963-967. 4. Sophian, L. H., and others: The Sulfapyrimidines, Press of A. Colish, New York, 1952.

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Supplied: Suspension SULFOSE: Bottles of 1 pint
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THE ORIGINAL ENTERIC-COATED TABLET OF THEOBROMINE SODIUM ACETATE



provides

EFFECTIVE
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PROLONGED
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in

CORONARY ARTERY DISEASE

REPEATEDLY SHOWN and proven by objective tests on human subjects[1] — this is one of the most effective of all the commonly known Xanthine derivatives. Because of the enteric coating it may be used with marked freedom from the gastric distress characteristic of ordinary Xanthine therapy. Thus **THESODATE**, with its reasonable prescription price also, enjoys a greater patient acceptability.

Available: **In bottles of 100, 500, 1000.**

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*(7½ gr.) 0.5 Gm. *(3¾ gr.) 0.25 Gm.

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*(7½ gr.) 0.5 Gm. with (½ gr.) 30 mg.
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*(3¾ gr.) 0.25 Gm. with (¼ gr.) 15 mg.

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(5 gr.) 0.3 Gm. with (2 gr.) 0.12 Gm.

THESODATE, POTASSIUM IODIDE WITH PHENOBARBITAL

(5 gr.) 0.3 Gm., (2 gr.) 0.12 Gm. with (¼ gr.) 15 mg.

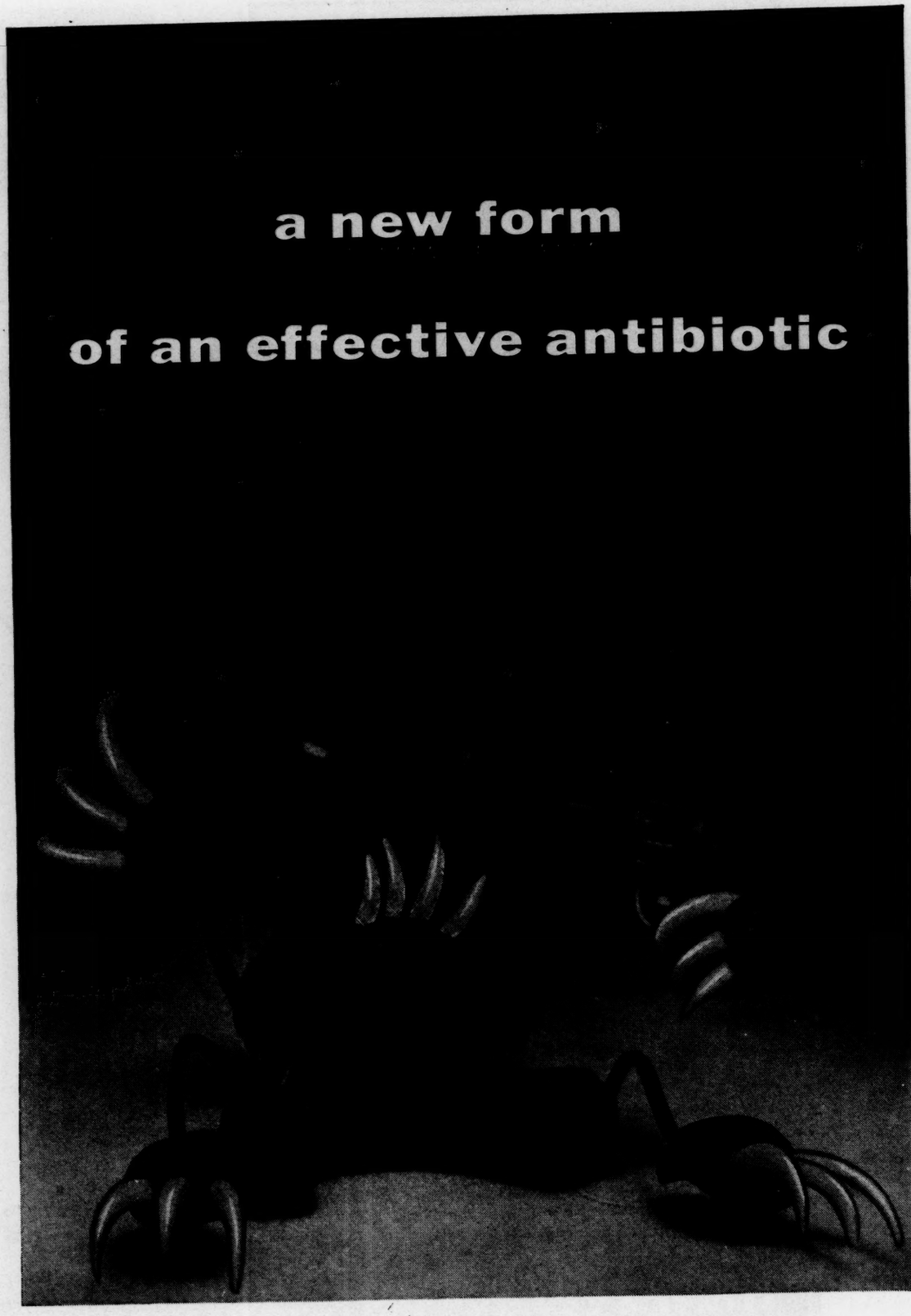
*In capsule form also, bottles of 25 and 100.

1. Riseman, J. E. F. and Brown, M. G. Arch. Int. Med. 60: 100, 1937
2. Brown, M. G. and Riseman, J. E. F. JAMA 109: 256, 1937.
3. Riseman, J. E. F. N. E. J. Med. 229: 670, 1943.

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New ERYTHROCIN Stearate tablets provide excellent drug protection from gastric secretions with the new *Film Seal** marketed only by Abbott—plus a special buffer system. Result: Because the need for an enteric coating is eliminated, the drug is more rapidly absorbed.

NOW . . . EARLIER BLOOD LEVELS

Because of the swift absorption, high blood concentrations of ERYTHROCIN are reached *within 2 hours.* (Enteric-coated erythromycin affords little or no blood level at 2 hours.) Peak level is reached at 4 hours, with significant concentrations for 8 hours.

LOW TOXICITY

ERYTHROCIN is *less likely to alter normal intestinal flora than most other widely-used antibiotics.* Gastrointestinal disturbances are rare, with no serious side effects reported.

EFFECTIVE AGAINST RESISTANT COCCI

ERYTHROCIN Stearate is highly effective against coccal infections. Especially recommended when the infecting organism is staphylococcus—*because of the high incidence of staphylococci resistant to penicillin and other antibiotics.* Advantageous, too, when patients are allergically sensitive to other antibiotics.

ERYTHROCIN Stearate (100 and 200 mg.) comes in bottles of 25 and 100 *Film Sealed* tablets. Abbott

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Pediatric ERYTHROCIN Stearate Oral Suspension. Tasty, stable, ready-mixed

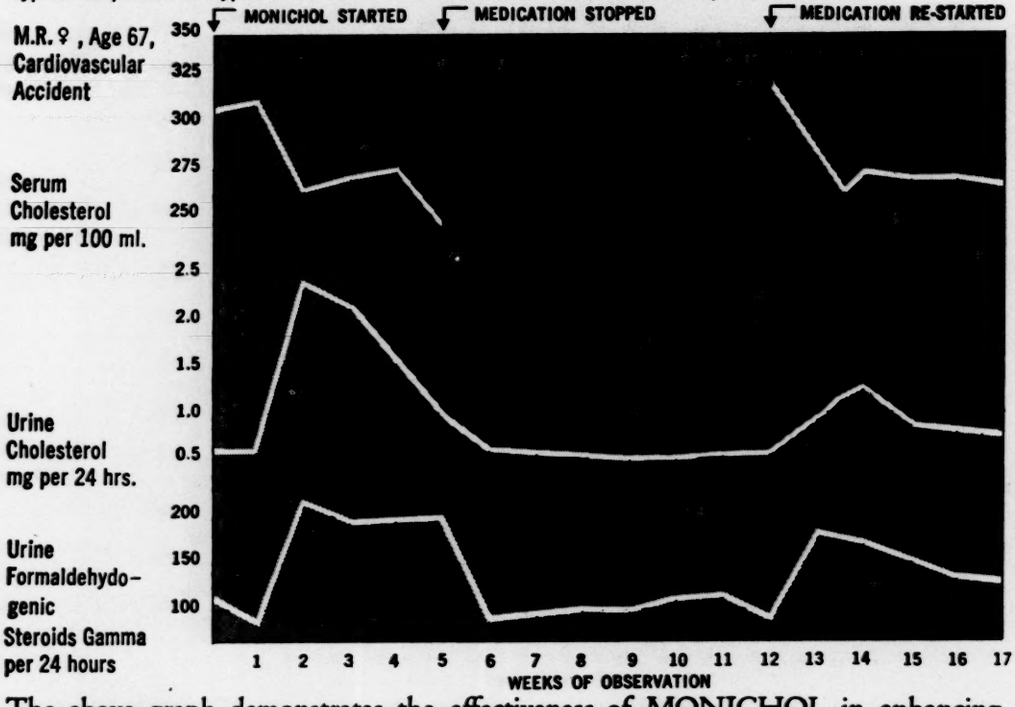
the realization of a hope . . .

. . . for a satisfactory preparation in the management of hypercholesteremia

MONICHOL*

IVC®

Typical Response of a Hypercholesteremic Patient to 20 cc. of MONICHOL* Daily in Divided Doses**



The above graph demonstrates the effectiveness of MONICHOL in enhancing the stability of the serum lipid emulsion by: ▲ normalizing elevated serum cholesterol levels, ● changing the character of the excess serum cholesterol to facilitate urinary excretion, and ■ making the excess serum cholesterol more readily available for utilization by the adrenal cortex in steroid synthesis.**

The sense of well-being experienced by patients on MONICHOL is attributed by the investigators** to better utilization of excess serum cholesterol by the adrenal cortex. MONICHOL is entirely non-toxic.

The red portion of the graph shows that uninterrupted daily intake of MONICHOL is essential, because hypercholesteremia is probably due to an inborn error of metabolism.

Indications: For the therapeutic and prophylactic management of hypercholesteremia so frequently associated with cardiovascular disease and diabetes.

Formula: Each teaspoonful (5 cc.) contains:		Minimum Dosage: Two teaspoonsful twice daily after meals.
Polysorbate 80	500 mg.	Supplied: Bottles of 12 oz.
Choline Dihydrogen Citrate	500 mg.	
Inositol	250 mg.	Literature on request

**Sherber, D. A., and Levites, M. M.: Hypercholesteremia. Effect on Cholesterol Metabolism of a Polysorbate 80-Choline-Inositol Complex (MONICHOL) J.A.M.A. 152:682 (June 20) 1953.

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Monichol normalizes cholesterol metabolism

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CAPSULES

significantly effective

Vertavis® and Vertavis-Phen®

In severely hypertensive patients with heart failure, Vertavis and Vertavis-Phen cause a significant improvement of total circulation, a transient increase in coronary flow, and a decrease in auricular pressure. Marked falls in blood pressure have resulted in the majority of patients.

In most cases, therapeutic doses of Vertavis or Vertavis-Phen can be given without gastrointestinal disturbances. Some patients, however, will exhibit side effects which are not of a serious nature and are easily overcome by reduction in dosage.

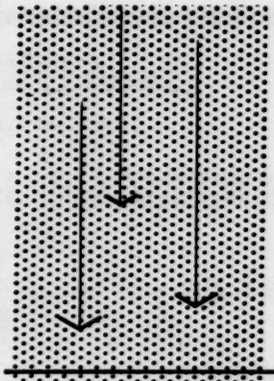
Dosage should start with 1 tablet twice daily, administered immediately after breakfast and at bedtime. If it is necessary to increase dosage, this routine should be modified to include an afternoon dose at 1:00 or 2:00 p.m. If further dosage increases are required in an occasional patient, the smallest dose should be taken at 1:00 or 2:00 p.m. and the largest dose at bedtime. The patient should refrain from eating for 4 hours after taking medication. Clinical studies show that the side effects from time and mode of administration may be minimized by adhering to the dosage schedule outlined above.

Long term treatment with Vertavis and Vertavis-Phen has resulted in the clearing of retinal hemorrhages and exudates of the optic fundi, in diminution of heart size as well as normalization of left ventricular strain patterns in the electrocardiogram.

IRWIN, NEISLER & COMPANY
DECATUR, ILLINOIS

STILL NO SAFER DRUG
IN SEVERE HYPERTENSION

characterized by marked elevation of diastolic blood pressure and signs and symptoms of vascular damage

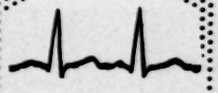




dilatation of spastic retinal arteries



improvement of cardiac efficiency and circulation



reversal of left ventricular strain pattern in the E.K.G.



diminution of cardiac size and marked subjective improvement of the patient

Experience has shown that Vertavis is singularly free of dangerous side actions. Vertavis, containing cryptenamine, the new broader safety ratio Veratrum alkaloid, can be administered continuously over extended periods of time without cumulative effects or postural hypotension. Marked subjective and objective improvement of the seriously ill patients has been observed.



Vertavis®

Each tablet contains: Whole-powdered Veratrum viride (containing cryptenamine) 130 C.S.R.* Units

*Carotid Sinus Reflex

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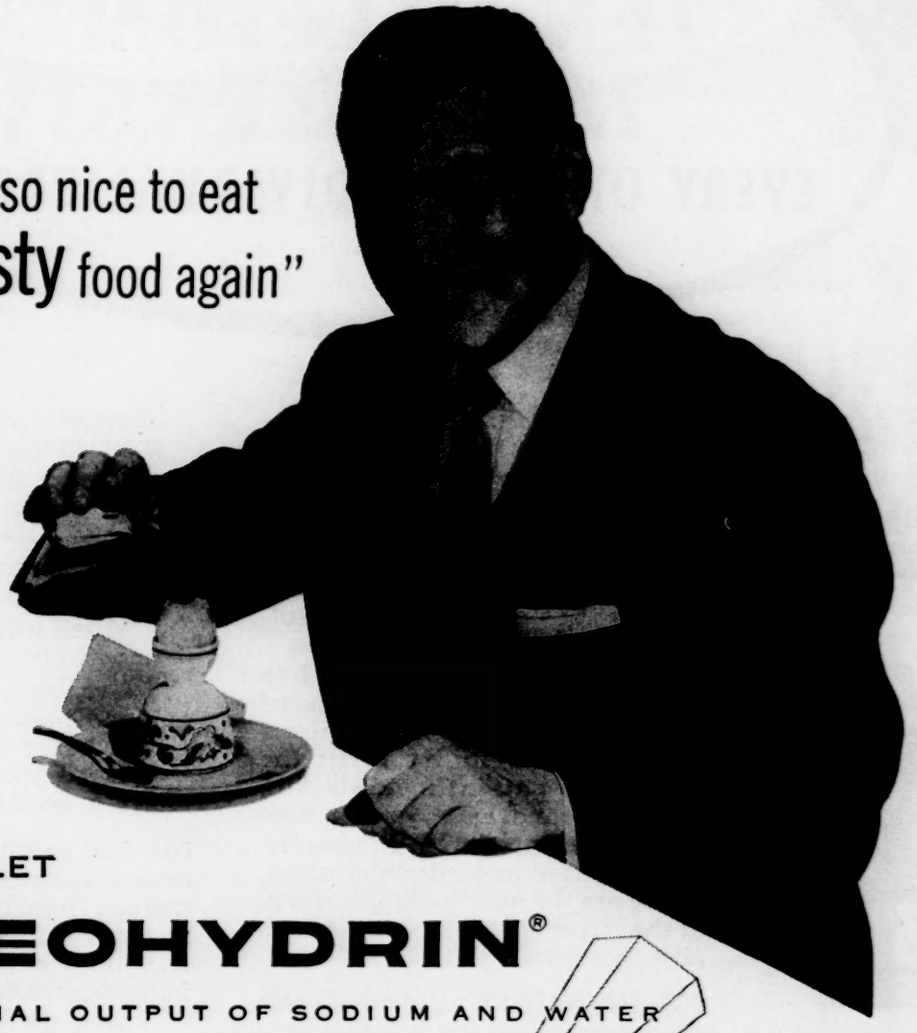
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PRESCRIBE NEOHYDRIN in bottles of 50 tablets. There are 18.3 mg. of 3-chloromercuri-2-methoxy-propylurea in each tablet.

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TEN MILLION HYPERTENSIVES

EVERY ONE AN INDIVIDUAL PROBLEM

HYPERTENSIVE DISEASE, widespread as it is today, cannot be defined as a discrete entity which responds universally to the administration of a single drug. It is a complex and dynamic disease process for which—in its several stages [1, 2, 3, 4]—no one drug will suffice or prove optimally effective.

Intensive Riker research has provided an armamentarium of drugs and drug combinations, embodying flexibility to fit the individual patient's needs and responses, and at the same time offering a completely new simplicity in dosage and administration. These are the outstanding features of the Riker approach to hypertensive therapy:

FOR THE PATIENT—Effective, safe drug therapy permits a fuller, happier life, less hampered by restrictions, and free from the need for heavy sedation.

Fewer dosage adjustments, with simpler, easier-to-follow dosage instructions.

Better prognosis regarding the deleterious influence of increasing pressure on the progression of the disease.

Greater freedom from hypertensive symptoms while under adequate therapy.

Apprehension allayed by tranquilizing effect of Rauwiloid.

Much lessened incidence of undesirable side effects.

Greater stability of lowered blood pressure makes chronic care safer and minimizes the possibility of escape from therapeutic levels.

FOR THE PHYSICIAN—For the first time, a complete spectrum of drug therapy for *all* hypertensives—in any stage of the disease—and with flexibility sufficient to adjust to individual response variations.

Ease of dosage adjustment makes patient supervision less cumbersome and more secure.

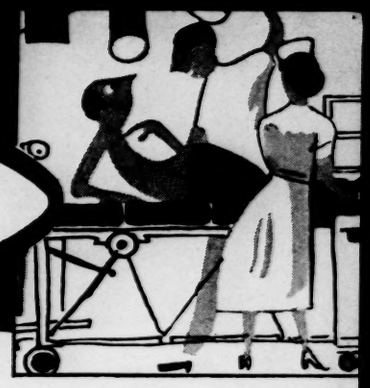
Proved clinical effectiveness with pharmacologically stable preparations.

Patient-acceptance of tablet therapy without complicated time schedules.

HERE IS

EFFECTIVE THERAPY

FOR EACH



IN GRADE I
RAUWILOID®

for Mild, Labile Hypertension

This selective alkaloidal extract (the alseroxylon fraction) of Rauwolfia serpentina provides effective treatment in the largest contingent of hypertensive patients—those with mild, labile hypertension.[5]

Rauwiloid produces:

- Dependable, gradual, temperate lowering of blood pressure.
- Subjective improvement and a sense of well-being occur within days, usually before full hypotensive effect is accomplished.
- A new type of gentle sedation—without somnolence.
- Virtually no side effects.
- No tolerance development.
- No danger of postural hypotension or excessive drop in blood pressure.
- No known contraindications.
- Dosage is not critical
- Simple dosage regimen: One dose of 2 tablets per day (2 mg. per tablet) taken on retiring usually suffices.

IN GRADES II and III
RAUWILOID + VERILOID
in a Single Tablet

for Moderate to Severe Hypertension

The combination of Rauwiloid with the faster-acting, more potent hypotensive—Veriloid®—provides effective therapy with least risk.

Apparent synergistic action of the combined drugs results in full hypotensive effects of Veriloid in well tolerated dosage.[6, 8]

- Dramatic, rapid symptomatic improvement when headache, dizziness and tachycardia are prominent.
- Side effects of Veriloid (nausea and vomiting) rarely encountered.
- Simpler plan of management with minimal dose adjustment and without loss of efficacy. Each tablet presents Rauwiloid 1 mg. and Veriloid 3 mg. Initial dose 1 tablet t.i.d., best after meals. Average maintenance dose, 1 tablet q.i.d.
- Addition of Rauwiloid increases percentage of patients in whom Veriloid proves effective.[7]

IN GRADES III and IV
RAUWILOID + HEXAMETHONIUM
in a Single Tablet

for Intractable, Rapidly Progressing Hypertension

When the patient's status warrants risking treatment by ganglionic blockade, addition of Rauwiloid's tranquilizing effect and gentle peristalsis stimulating action reduce erratic response inherent in hexamethonium therapy.[9, 10] Symptoms rapidly yield and tachycardia is relieved by mild bradycardic action of Rauwiloid.

Apparent synergistic action of Rauwiloid results in full hypotensive effect of hexamethonium from greatly reduced dosage (up to 50% less).[9]

Cautions and contraindications are only those applying to hexamethonium; but diligent patient supervision and careful instruction of the patient remain mandatory.

Each tablet contains Rauwiloid 1 mg. and hexamethonium 250 mg. Therapy should be initiated with ½ tablet q.i.d., not less than 4 hours apart, best before meals and at bedtime. After two weeks, when Rauwiloid effect has been established, dosage should be increased by 1 tablet per day, not oftener than twice weekly, until desired effect is obtained.

IN HYPERTENSIVE CRISES

Encephalopathy... Eclampsia

Solution Intravenous Veriloid* and Solution Intramuscular Veriloid* provide for immediate control of the critical blood pressure; they should be followed by carefully selected, adequate oral therapy based on prognosis.

*N.N.R.

Riker LABORATORIES, INC.

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for the obese patient . . .





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obtainable
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tablets are
monogramed
for your
assurance of
quality

Obedrin

Semoxydrine HCl ..... (Methamphetamine HCl)	5 mg.
Pentobarbital	20 mg.
Ascorbic Acid	100 mg.
Thiamine HCl	0.5 mg.
Riboflavin	1 mg.
Niacin	5 mg.

massengill

BIOPAR

intrinsically better

BIOPAR

supplements
spaces out
replaces
} B_{12} injections

BIOPAR®

vitamin B_{12}
and
intrinsic factor Armour

Each Biopar tablet supplies:
Vitamin B_{12}
Crystalline U.S.P... 6 mcg.
Intrinsic Factor..... 30 mg.



THE ARMOUR LABORATORIES

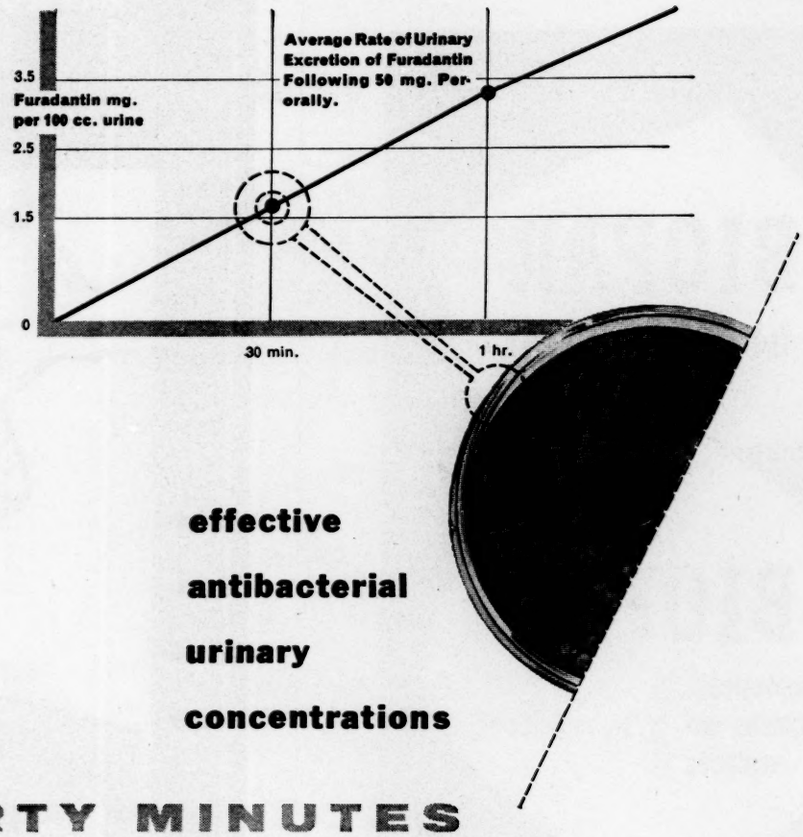
IMPROVED RELAXATION THERAPY



Mephate 'Robins' relaxes skeletal muscle spasm and tremor without impairing strength; and allays nervous tension and anxiety without dimming consciousness. • Mephate (0.25 Gm. of mephenesin and 0.30 Gm. of glutamic acid hydrochloride in each capsule) has been shown to be more effective clinically than mephenesin alone.

MEPHATE Robins
CAPSULES

Ethical Pharmaceuticals of Merit since 1866



effective antibacterial urinary concentrations

IN THIRTY MINUTES

So remarkable is the affinity of Furadantin for the urinary tract that the urine becomes actively antibacterial within 30 minutes after ingestion, as shown by urinary concentrations and agar plate tests.

Furadantin exhibits an extensive range of antibacterial activity against both gram-positive and gram-negative urinary tract invaders.

Scored tablets of 50 & 100 mg.

IN ACUTE AND CHRONIC URINARY INFECTIONS

FURADANTIN®

BRAND OF NITROFURANTOIN, EATON

ACCEPTED COUNCIL ON PHARMACY AND CHEMISTRY AMERICAN MEDICAL ASSOCIATION

EATON LABORATORIES Inc.

NORWICH, NEW YORK

THE NITROFURANS—A UNIQUE CLASS OF ANTIMICROBIALS O_2N [ring] R PRODUCTS OF EATON RESEARCH

In Neuritis—

is temporary relief enough?

Now—



THE LONG PERIOD OF DISTURBING SYMPTOMS CAN BE REDUCED BY THE PROMPT USE OF—

PROTAMIDE

When you have a case of neuritis (intercostal, facial or sciatic) where the inflammation of nerve roots is not caused by mechanical pressure, let Protamide demonstrate how much faster lasting relief can be obtained than with usual therapy.

Usual dose: one ampul every day for five days or longer.

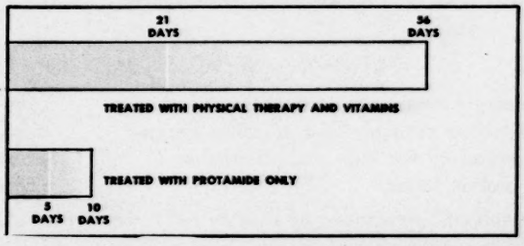
NEURITIS

(Sciatic • Intercostal • Facial)

A COMPARISON BETWEEN COMPARABLE GROUPS WITH AND WITHOUT PROTAMIDE THERAPY

CONTROL—158 Patients
The Course of the Disease Was 21 Days to 56 Days

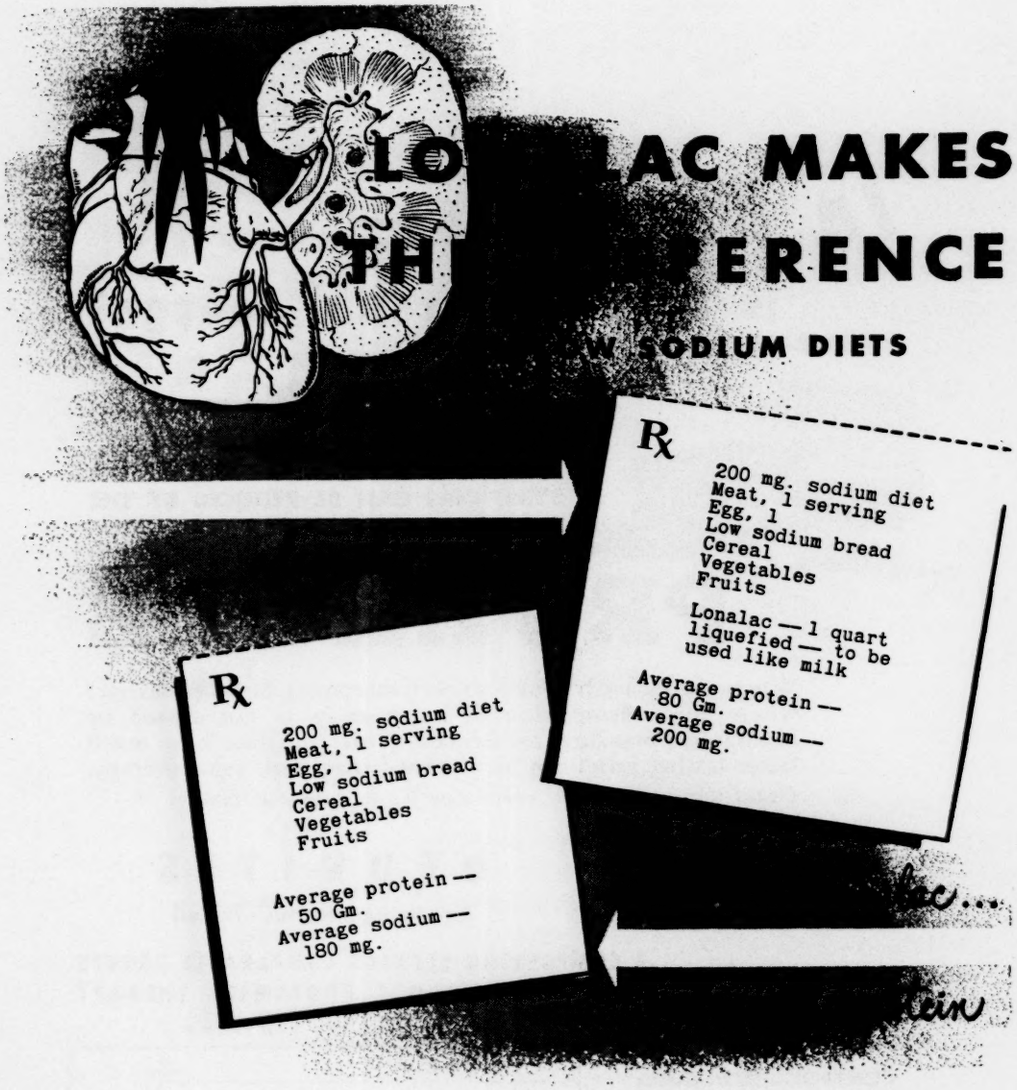
PROTAMIDE—84 Patients
Complete Relief was Obtained in 5 to 10 Days



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"TREATMENT OF NEURITIS WITH PROTAMIDE"
Richard T. Smith, M.D.
Associate in Medicine and Chief of Arthritis at Jefferson Medical College and Hospital; Associate Physician and Chief of Arthritis, Pennsylvania Hospital; Director of Department of Rheumatology, Benjamin Franklin Clinic.

REPRINTS AVAILABLE



Nutritionally similar to whole milk but with negligible sodium content, Lonalac solves the problem created by the high sodium content of the usual protein foods.

When sodium intake must be sharply restricted, protein deficiency is seriously threatened . . . since meat and eggs can be used only in small quantities and milk, with its still higher sodium content, usually must be eliminated.

With Lonalac supplying the protein equivalent of milk, the patient's nutritional needs can be generously met, even on a 200 mg. sodium diet.

Lonalac is used just as milk is used, as a beverage and in soups, muffins, desserts, etc. It permits varied and appetizing meals that encourage patients to adhere to a low sodium regimen.

Lonalac is virtually free of cholesterol.

Lonalac is supplied in 1 pound and economical 4 pound cans. Low sodium diet outlines suitable for use by patients are available on request.

Lonalac

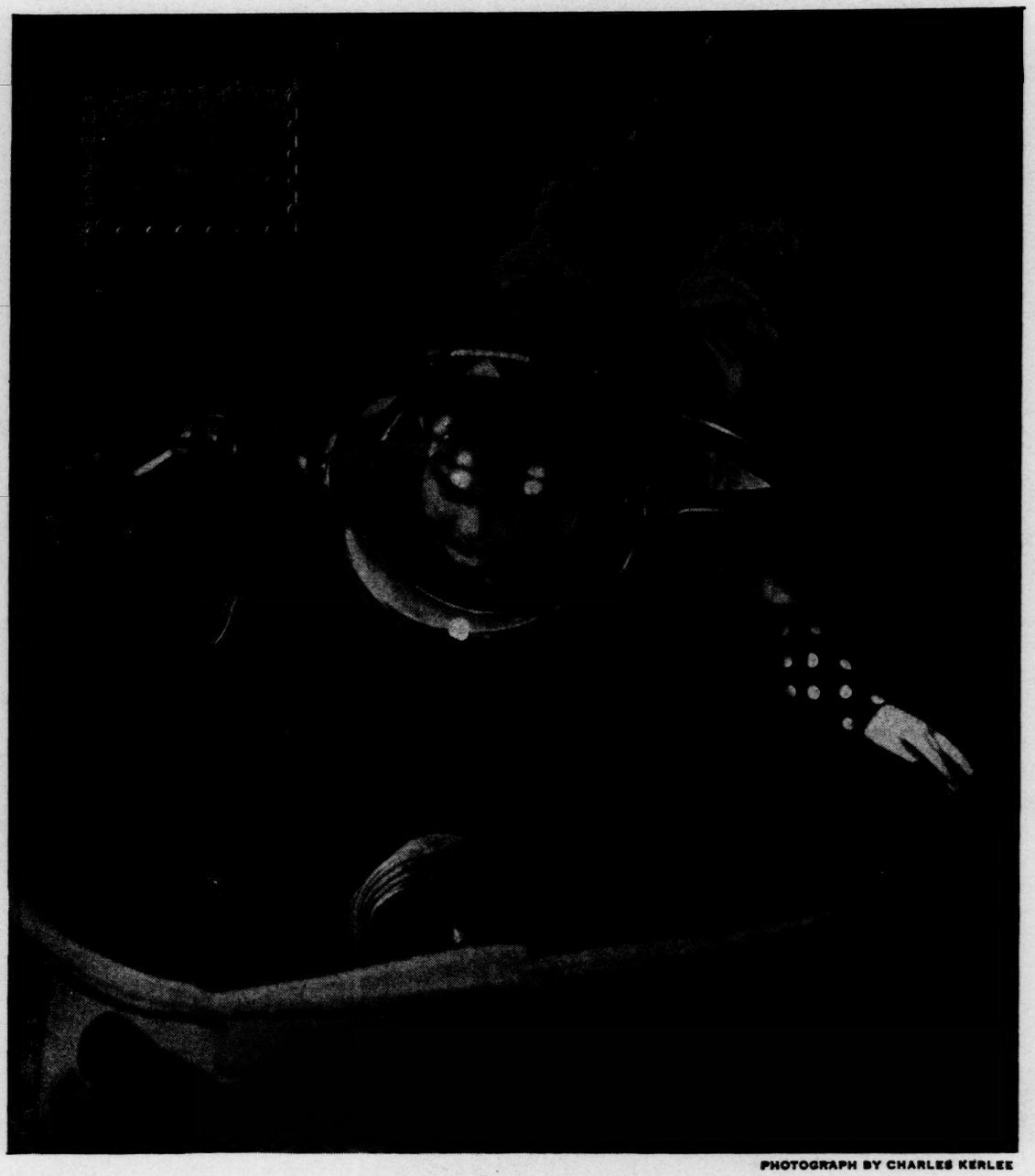
The low sodium, high protein food

MEAD JOHNSON & COMPANY • EVANSVILLE, INDIANA, U.S.A. MEAD

AMPHEDASE*



Parke, Davis & Company



PHOTOGRAPH BY CHARLES KERLEE

Bounces back to normal with

PENTRESAMIDE®

TRIPLE SULFONAMIDE WITH PENICILLIN

Serious infections of mixed bacterial origin respond so rapidly to PENTRESAMIDE that your patients seem almost to bounce back to normal. Even in pneumonia, a single oral dose of this established antibiotic-sulfonamide produces "striking therapeutic results."[1] Easy-to-take, it is especially suitable for children.

Quick Information: PENTRESAMIDE-100 and PENTRESAMIDE-250 *Tablets* provide in each tablet 0.1 *Gm.* sulfamerazine, 0.2 *Gm.* each sulfamethazine and sulfadiazine with 100,000 or 250,000 units potassium penicillin G. Dosage schedules on request.

Reference: 1. New York State J. Med. 50:2293, 1950.



new for people who travel

Bonamine*

Brand of meclizine hydrochloride

the first compound effective against motion sickness in a single daily dose

most prolonged action

Bonamine is the only motion-sickness preventive which is effective in a *single daily dose.* Just two 25 mg. tablets (50 mg.) will provide adequate protection against all types of motion sickness—car or boat, train or plane—for a *full 24 hours in most persons.*

few side effects

Clinical studies have shown, in case after case, that relatively few of the patients experienced the usual side effects observed with other motion-sickness remedies: less drowsiness, dullness, headache, dryness of the mouth, etc. In addition, Bonamine is tasteless and acceptable to patients of all ages.

Supplied: 25 mg. tablets.

*TRADEMARK

Pfizer

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Division, Chas. Pfizer & Co., Inc.



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SENSIBLE
DIETING

with

Am Plus®

curb appetite To reduce voluntary food intake, every AM PLUS capsule provides 5 mg. of dextro-amphetamine sulfate

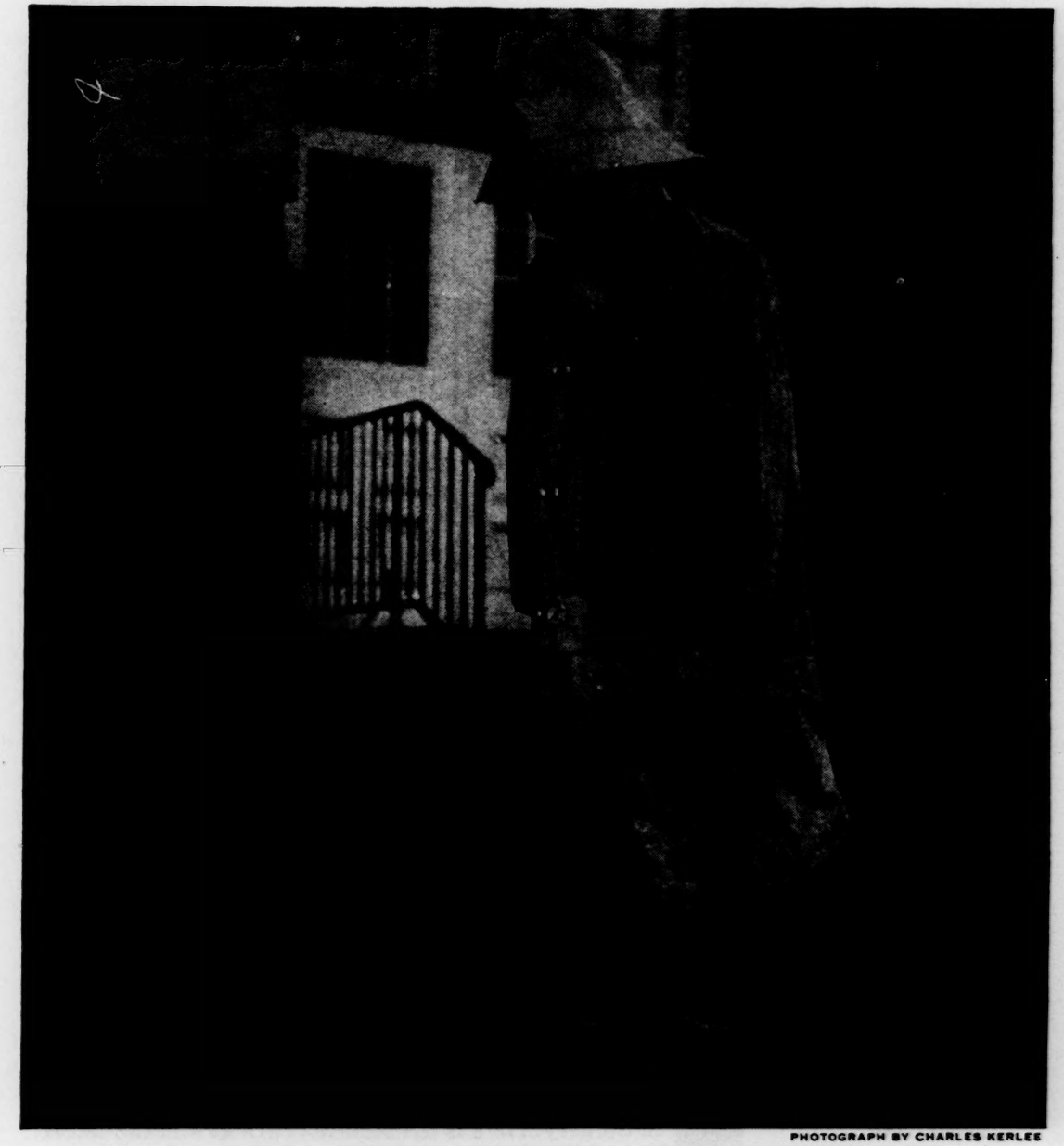
while maintaining

sound nutrition The balanced AM PLUS formula assures adequate vitamin-mineral supply, essential in any weight control program

each capsule of *Am Plus* contains:

DEXTRO-AMPHETAMINE SULFATE	5 mg.
Vitamin A	5,000 U.S.P. Units
Vitamin D	400 U.S.P. Units
Thiamine Hydrochloride	2 mg.
Riboflavin	2 mg.
Pyridoxine Hydrochloride	0.5 mg.
Niacinamide	20 mg.
Ascorbic Acid	37.5 mg.
Calcium Pantothenate	3 mg.
Calcium	242 mg.
Cobalt	0.1 mg.
Copper	1 mg.
Iodine	0.15 mg.
Iron	3.33 mg.
Manganese	0.33 mg.
Molybdenum	0.2 mg.
Magnesium	2 mg.
Phosphorus	187 mg.
Potassium	1.7 mg.
Zinc	0.4 mg.

J. B. ROERIG AND COMPANY, *Chicago 11, Illinois*



PHOTOGRAPH BY CHARLES KERLEE

For recurrent rheumatic fever prophylaxis . . .

PENALEV®

SOLUBLE TABLETS POTASSIUM PENICILLIN G

Recurrences of rheumatic fever may be avoided by year-round use of PENALEV. Accumulated evidence "indicates that oral penicillin is a safe and effective prophylactic agent . . . no penicillin-resistant strains of group A hemolytic streptococci have been reported,"[1] following oral doses of penicillin. The onset of rheumatic fever may be prevented by treating streptococcal infections with large doses of oral penicillin.[2]

Readily soluble in ordinary beverages, PENALEV is easy to take over long periods.

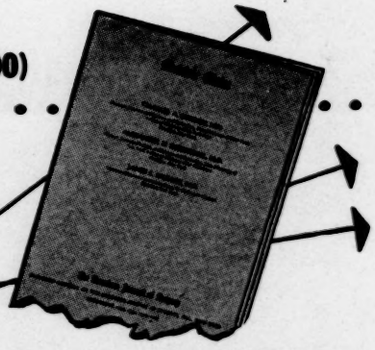
Quick Information: *Supplied* in soluble tablets of 50,000, 100,000, 200,000, 250,000, 500,000 and 1,000,000 units of potassium penicillin G.

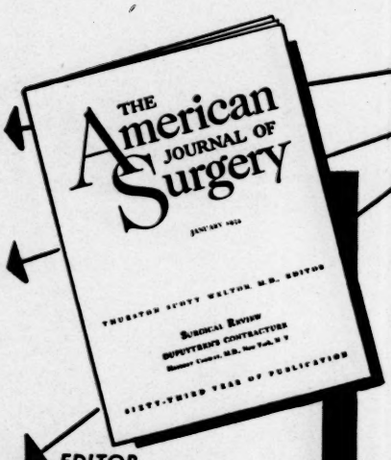
References: 1. Postgrad. Med. 14:429, 1953.
2. J.A.M.A. 151:141, 1953.

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Each SUR-BEX Tablet Contains:

Thiamine Mononitrate	6 mg.
Riboflavin	6 mg.
Nicotinamide	30 mg.
Pyridoxine Hydrochloride	1 mg.
Vitamin B_{12}	2 mcg.
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Liver Fraction 2, N.F.	0.3 Gm. (5 grs.)
Brewer's Yeast, Dried	0.15 Gm. (2½ grs.)

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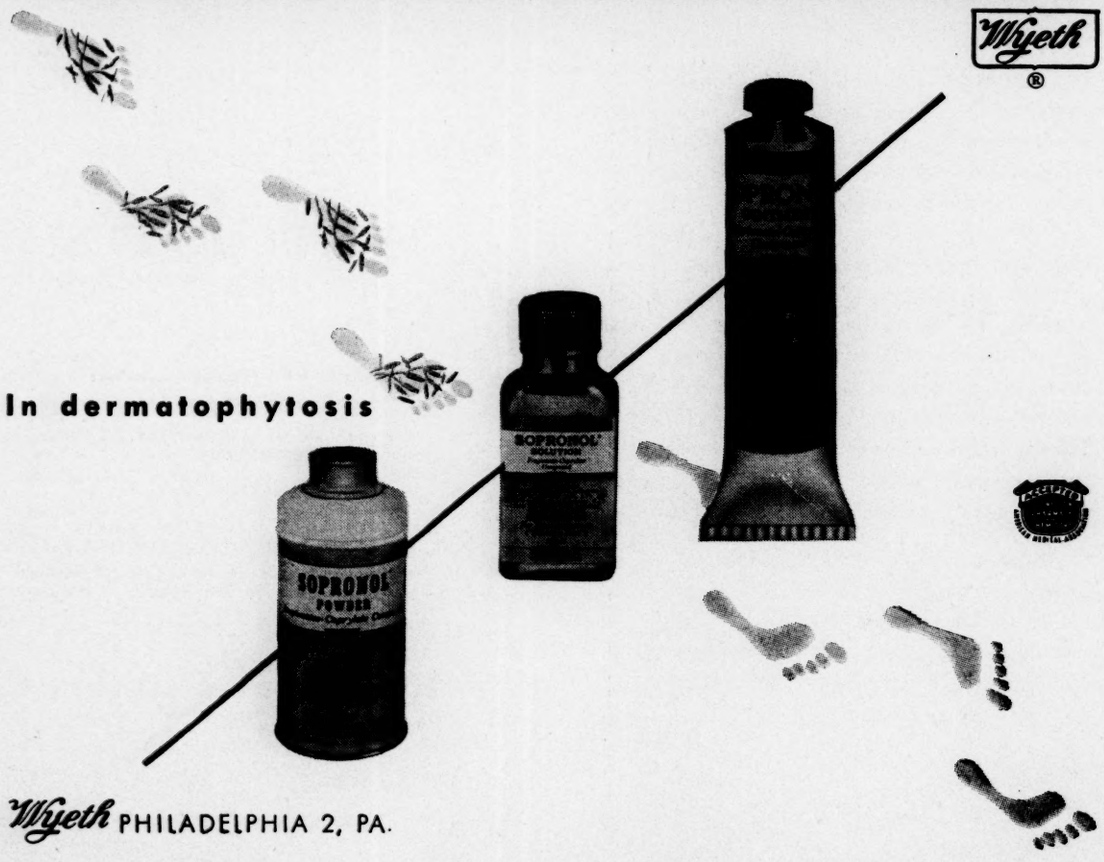
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Wyeth®



In dermatophytosis

Wyeth PHILADELPHIA 2, PA.



PHOTOGRAPH BY CHARLES KERLEE

Gives "remarkable increase in strength, vigor"[1]...

REDISOL®

CRYSTALLINE VITAMIN B_{12}

In "pernicious anemia or tropical sprue in relapse," not even blood transfusions give the "remarkable increase in strength, vigor and appetite,"[1] induced by vitamin B_{12}.

REDISOL—vitamin B_{12}—has hemopoeitic activity of liver[2]; improves neurologic symptoms; no evidence of toxicity.[2] Valuable in trigeminal neuralgia to relieve pain.

Quick Information: *Tablets,* 25 and 50 *mcg.; Injectable,* 30, 100 and 1000 *mcg.* per cc.; *Elixir, 5 mcg.* per 5 cc.

References: 1. J.A.M.A. 153:185, 1953: 2. N.N.R. 1953, p. 486.

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oral
estrogen-progesterone
effective in
menstrual disturbances:

Cyclogesterin
TRADEMARK, REG. U. S. PAT. OFF.
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Each scored tablet contains:

Estrogenic Substances* .. 1 mg.
(10,000 I.U.)

Progesterone .....30 mg.

**Naturally-occurring equine estrogens (consisting primarily of estrone, with small amounts of equilin and equilenin, and possible traces of estradiol) physiologically equivalent to 1 mg. of estrone.*

Available in bottles of 15 tablets.

The Upjohn Company, Kalamazoo, Michigan



"THIOSULFIL"
eliminates the need for forcing fluids

"THIOSULFIL"
makes alkalinization unnecessary

"THIOSULFIL"
greatly minimizes risk of sensitization

"THIOSULFIL"
drastically reduces likelihood of toxic side effects

"THIOSULFIL"
quickly provides effective bacteriostatic concentrations
at the site of infection

"THIOSULFIL"®
Brand of sulfamethylthiadiazole

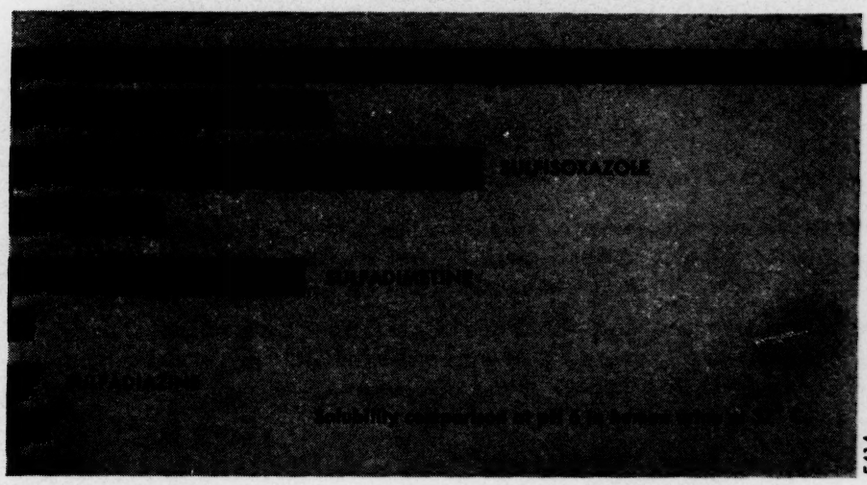
The safest and most effective sulfonamide yet presented for

URINARY TRACT INFECTIONS

TABLETS — No. 785—0.25 Gm. per tablet (scored)
Bottles of 100 and 1,000

No. 914—0.25 Gm. per cc. — **SUSPENSION**
Bottles of 4 and 16 fluidounces

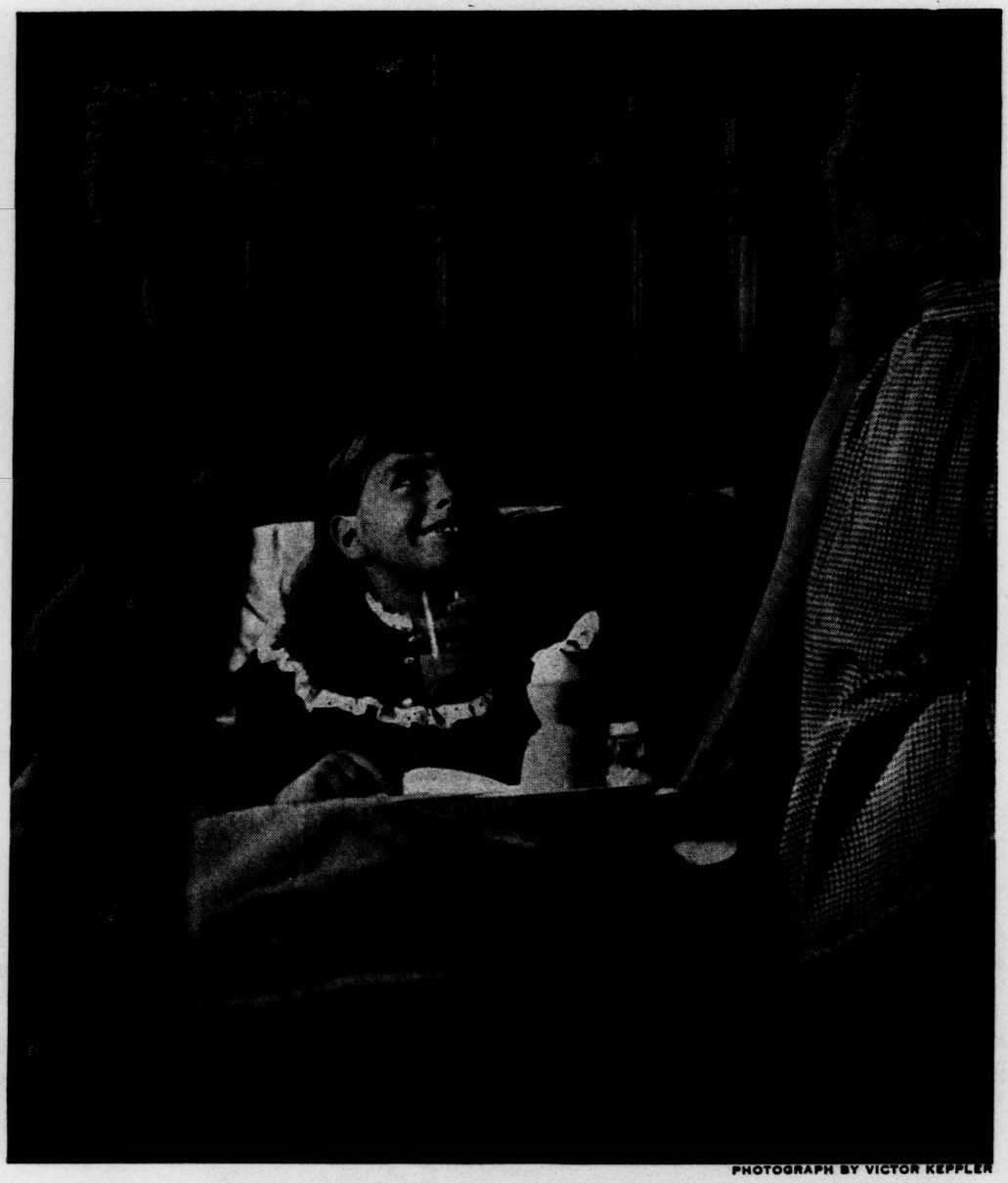
Note in chart below solubility of "Thiosulfil" when compared with the other three most frequently prescribed sulfonamides in urinary tract infections. Greater solubility means rapid action with minimum toxicity.



New York, N. Y.

Ayerst

Montreal, Canada



PHOTOGRAPH BY VICTOR KEPPLER

"Now I can swallow easily—my throat's much better"

TRACINETS®

BACITRACIN-TYROTHRICIN TROCHES WITH BENZOCAINE

Your patients will like TRACINETS because they really soothe irritated throats—taste good, besides.

Two topical antibiotics combined, bacitracin and tyrothricin, give your patients double antibacterial action, while benzocaine provides a soothing, anesthetic effect. In severe throat infections, TRACINETS conveniently supplement systemic therapy.

Quick Information: Each troche contains 50 units of bacitracin, 1 mg. of tyrothricin, 5 mg. of benzocaine. In vials of 12.

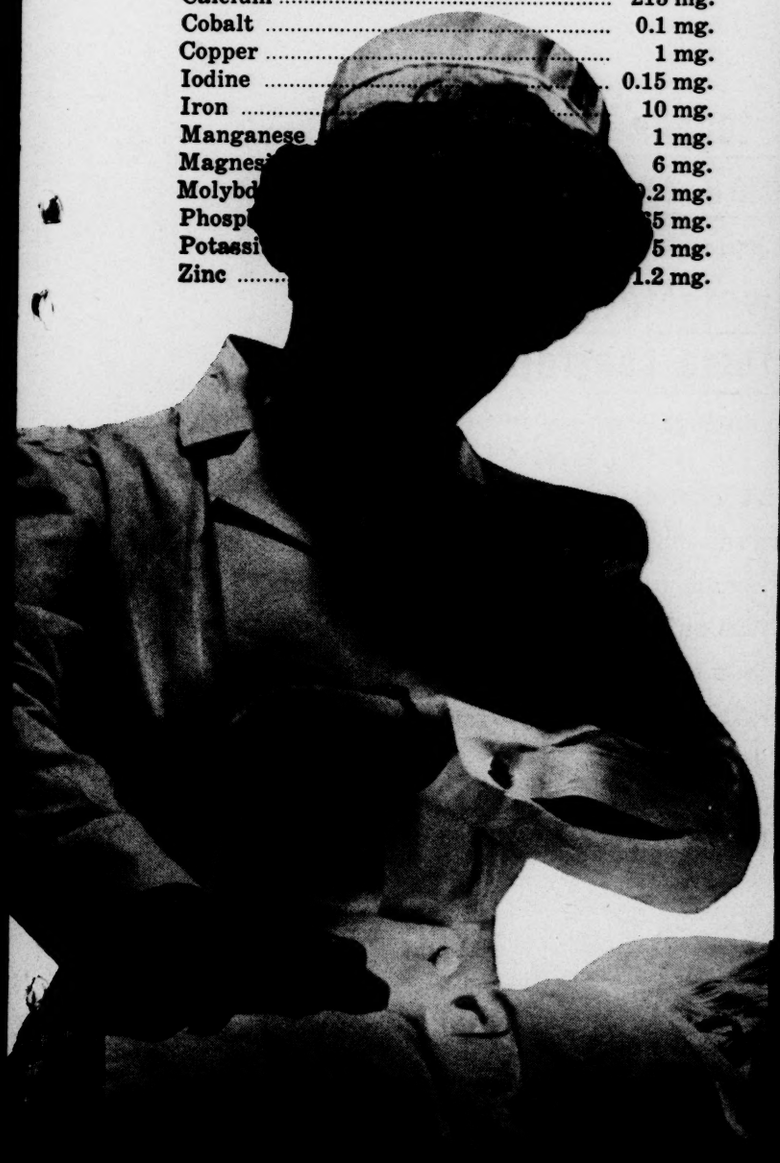
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a vitamin-mineral formulation of 21 balanced factors, supplementing the depleted diet

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Vitamin D	500 U.S.P. Units
Vitamin B_{12}	1 mcg.
Thiamine Hydrochloride	3 mg.
Riboflavin	3 mg.
Pyridoxine Hydrochloride	0.5 mg.
Niacinamide	25 mg.
Ascorbic Acid	50 mg
Calcium Pantothenate	5 mg.
Mixed Tocopherols *(Type IV)*	5 mg.
Calcium	213 mg.
Cobalt	0.1 mg.
Copper	1 mg.
Iodine	0.15 mg.
Iron	10 mg.
Manganese	1 mg.
Magnesi	6 mg.
Molybd	.2 mg.
Phospl	5 mg.
Potassi	5 mg.
Zinc	1.2 mg.



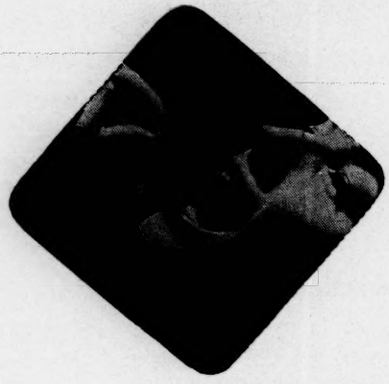
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First, under tongue for quick asthma relief

from aludrine (Isopropyl arterenol) HCl in coating

Then, swallow tablet for prolonged asthma control

from theophylline, ephedrine, phenobarbital, contained in tablet core

NEPHENALIN, the "relay-action" tablet combining two widely prescribed, complementary anti-asthmatics, is now available in two potencies: the familiar square, *purple* tablet for adults, and the smaller square, *red* tablet for children. Since a single NEPHENALIN tablet provides quick asthma relief, thereby often replacing the nebulizer, and since relief lasts about four hours, many asthmatic patients will find it the most convenient and efficient anti-asthmatic they have ever used. Bottles of 20 and 100 tablets.

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